Supporting Information

Complementary Hetrogeneous/Homogeneous Protocols for the Synthesis of Densely Functionalized Benzo[d]sultams: C-C Bond Formation by Intramolecular Nucleophilic Aromatic Fluorine Displacement

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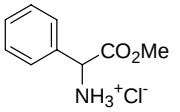
CONTENTS

Materials and Methods.

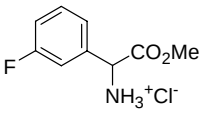
All reactions were carried out in flame-dried glassware with magnetic stirring. Isolated yields refer to homogeneous materials (TLC, HPLC, NMR). Reagent-grade commercially available reagents and solvents were used; anhydrous solvents (DMSO, MeCN, DME, NMP, and DMPU) were used as purchased. TLC was performed using 0.25 mm silica-gel pre-coated plates and visualized by UV-254 light and CAM staining. Silica-gel (particle size 0.040–0.063 mm) was used for flash column chromatography (FCC) and medium pressure liquid chromatographic (MPLC). Melting points are corrected. HPLC analyses were performed using an EC 250/4.6 NUCLEOSIL 100-5 column and, for chiral HPLC analyses, a 250/4.6 Chiracel OD column. IR spectra are reported in frequency of absorption (cm^{-1}). $[\alpha]_D$'s were measured at 589 nm, using a 10 cm x 5 ml cell and *c* is in g/100 ml. NMR spectra were recorded at: 500.13, 300.13 and MHz for ^1H; 125.77, 75.00 MHz for ^{13}C; 282.407 MHz for ^{19}F. TMS was used as external reference; δ are in ppm and *J* are in Hz.

Amino-arylacetic Acids and Methyl Amino-arylacetate Hydrochlorides

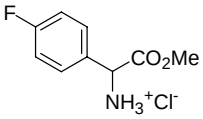
Starting amino-phenyl-,[1] amino-(3-fluoro-phenyl)-,[2] amino-(4-fluoro-phenyl)-,[1,2] amino-(4-chlorophenyl)-,[1,2] amino-(4-bromo-phenyl)-,[1] amino-*p*-tolyl-,[2] amino-(3-methoxy-phenyl)-,[1] amino-(4-methoxy-phenyl)-,[2] and amino-(4-benzyloxy-phenyl)-acetic acids[3] were synthesised following literature methods, amino-(thiophen-3-yl)-acetic acid was purchased from Sigma. The α-amino acids were then converted into the corresponding methyl ester hydrochlorides by reaction with $SOCl_2$ and dry MeOH,[4] whereas L-phenylglycine methyl ester hydrochloride was purchased from Aldrich. To compare with literature products, several free esters were obtained by neutralization of the corresponding hydrochlorides with cold, saturated $NaHCO_3$ solution and Et_2O extraction. The physical and/or spectroscopic characteristics of the isolated products are as follows.



Methyl amino-phenylacetate hydrochloride. Mp 220-223 °C (dec.) (lit.[5] mp 223-224 °C).



Methyl amino-(3-fluorophenyl)-acetate hydrochloride. Free amino ester, oil (lit.[6] 21 °C).



Methyl amino-(4-fluorophenyl)-acetate hydrochloride. Free amino ester, mp 37-38 °C (lit.[6] mp 39 °C).

(1) Landini, D.; Penso, M. *J. Org. Chem.* **1991**, *56*, 420.
(2) Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1979**, 26.
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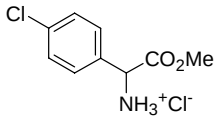
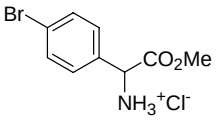
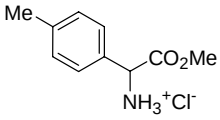
(4) Kihlberg, T.; Karimi, F.; Laengstroem, B.; *J. Org. Chem.* **2002**, *67*, 3687.
(5) Kyba,E. P.; Timko, J. M.; Kaplan, L. J.; De Jong, F.; George W. Gokel,G. W.; Cram, D. J. *J. Am. Chem. Soc.*, **1978**, *100*, 4555.
(6) Litvinenko, L. M.; Sharanin, Yu. A.; Bilobrova, A. I.; Drizhd, L. P. *Zh. Org. Khim.*; **1973**, *9*, 986. *J. Org. Chem. USSR (Engl. Transl.)*, **1973**, *9*, 1012.



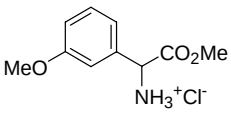
Methyl amino-(4-chlorophenyl)-acetate hydrochloride. Mp 193-196 °C (dec.) (lit.[7] 194-197 °C).



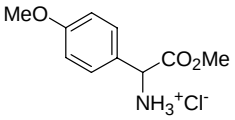
Methyl amino-(4-bromophenyl)-acetate hydrochloride. Free amino ester, mp 54 °C (lit.[6] 54 °C).



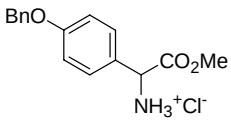
Methyl amino-*p*-tolyl-acetate hydrochloride. Mp 192-193 °C (dec.). ^{1}H NMR (300 MHz, D_2O) δ 7.37 (s, 4H), 5.26 (s, 1H), 3.83 (s, 3H), 2.87 (s, 3H).[8] Anal. Calcd. for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found C, 55.72; H, 6.56; N, 6.44.



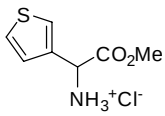
Methyl amino-(3-methoxyphenyl)-acetate hydrochloride. Mp 182-183 °C (dec.). ^{1}H NMR (300 MHz, D_2O) δ 7.50 (t, 1H, J = 8.0 Hz), 7.17-7.09 (m, 3H), 5.29 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H). Anal. Calcd. for $C_{10}H_{14}ClNO_3$: C, 51.84; H, 6.09; N, 6.05. Found: C, 51.80; H, 6.13; N, 6,09.



Methyl amino-(4-methoxyphenyl)-acetate hydrochloride. Mp 185-187 °C (dec.) (lit.[9] 187-189 °C).



Methyl amino-(4-benzyloxyphenyl)-acetate hydrochloride. Mp 210-212 °C (dec.) (lit.[10] 212-213 °C).

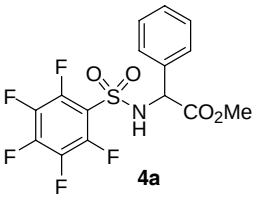


Methyl amino-(thiophen-3-yl)-acetate hydrochloride. Mp 230-232 °C (dec.). ^{1}H NMR (300 MHz, CD_3OD) δ 7.63 (d, 1H, J = 3.0 Hz), 7.30 (dd, 1H, J = 5.1, 3.0), 7.12 (d, 1H, J = 5.1 Hz), 5.50 (s, 1H), 3.85 (s 3H).[11] Anal. Calcd. for $C_7H_{10}ClNO_2S$: C, 40.48; H, 4.85; N, 6.74. Found C, 40.52; H, 4.88; N, 6.69.

(7) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1976**, *98*, 3038.
(8) ^{1}H NMR spectrum of the free ester: Rose-Munch, F.; Aniss, K.; Rose, E.; Vaisserman, J. *J. Organomet. Chem*. **1991**, *415*, 223.
(9) Baumgarten, H. E.; Dirks, J. E.; Petersen, J. M.; Zey, R. L. *J. Org. Chem.* **1966**, *31*, 3708.
(10) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563.
(11) Bateson, J. H.; Witty, D. R.; Gasson, B. C.; Best, D. J.; Payne, D. J. *WO* 9730027, **1997**; *Chem. Abstr.* **1997**, *127*, 220985.

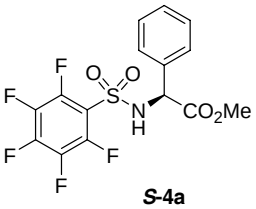
Synthesis of (Pentafluorobenzene)sulfonamides 4a-j: General Procedure

To a suspension of methyl 2-arylacetate hydrochloride (10 mmol) in dry dichloromethane (40 mL), DIPEA (21 mmol) was added at 25 °C in 10 min. The reaction mixture was stirred for furhter 10 min, then cooled to 0°C and pentafluorobenzenesulfonyl chloride (10 mmol) was added dropwise. The resulting solution was allowed to reach 25 °C and stirred until no starting material was not detectable by TLC, then was diluted with dichloromethane (20 mL), washed with 3% HCl (3×15 mL), saturated $NaHCO_3$ solution (2×15 mL) and brine (20 mL), dried over $MgSO_4$, filtered. After evaporation of the solvent under vacuum (RV), the crude recrystallized from ethanol/water (1 : 9), or purified by FCC or MPLC, gave sulfonamides **4a-j**. Starting material, product, yield, chromatographic eluant, physical and analytical data are as follows.



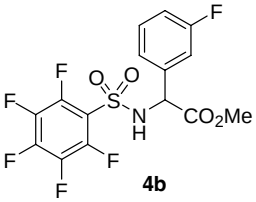
4a

Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (4a). Methyl 2-amino-2-phenylacetate hydrochloride, 2.02 g . **4a** (3.56 g, 90%); white solid, mp 120-121°C (EtOH/water – 9 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.19 (m, 5H), 6.42 (d, 1H, *J* = 7.5 Hz,), 5.28 (d, 1H, *J* = 7.5 Hz), 3.72 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.9 (m, 1F), -159.8 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 143.9 (dm, *J* = 258.6 Hz), 143.6 (dm, *J* = 261.6 Hz), 137.4 (dm, *J* = 258.4 Hz), 133.8, 129.2, 128.9, 127.3, 116.7, 59.9, 53.4. IR (nujol) 3331, 1741, 1644, 1522, 1300, 1214, 1101, 985, 885 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}F_5NO_4S$: C, 45.58; H, 2.55; N, 3.54. Found: C, 45.52; H, 2.58; N, 3.59. (chiral HPLC analysis see page S56).



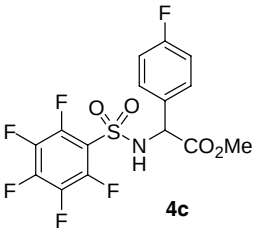
***S*-4a**
(ee >99%)

***S*-Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (*S*-4a).** Analogous preparation to that of **4a**, starting from L-phenylglycine methyl ester hydrochloride. White solid, mp 120 °C; $[\alpha]_D^{20}$ +79.8 (*c* 1, $CHCl_3$). NMR spectra match those of **4a**. (see page S-58 for chiral HPLC analysis).



4b

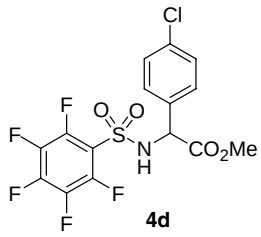
Methyl 2-(3-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4b). Methyl 2-amino-2-(3-fluorophenyl)acetate hydrochloride, 2.20 g. **4b** (3.35 g, 81%); white solid, mp 108.5-109.5°C (EtOH/water – 9 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 1 H), 7.05-6.92 (m, 3 H), 6.34 (d, 1H, *J* = 7.4 Hz), 5.27 (d, 1H, *J* = 7.4 Hz), 3.73 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.3 (s, 1F), -136.5 (m, 2F), -146.1 (m, 1F), -159.3 (m, 2F). IR (nujol) 3238, 1747, 1643, 1519, 1329, 1201, 1101, 991, 897 cm^{-1}. Anal. Calcd. for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19; F, 27.58; N, 3.39. Found: C, 43.63; H, 2.15; N, 3.41.



4c

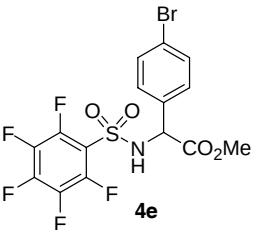
Methyl 2-(4-fluorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4c). Methyl 2-amino-2-(4-fluorophenyl)acetate hydrochloride, 2.20 g. **4c** (3.30 g, 80%); white solid, mp 125-126 °C (EtOH/water – 9 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.20 (m, 2H), 6.99-6.93 (m, 2H), 6.30 (d, 1H, *J* = 7.2 Hz), 5.27 (d, 1H, *J* = 7.2 Hz), 3.71 (s, 3H). ^{19}F

NMR (282 MHz, $CDCl_3$) δ -111.6 (s, 1F), -136.5 (m, 2F), -146.1 (m, 1F), -159.4 (m, 2F). IR (nujol) 3274, 1746, 1649, 1520, 1305, 1171, 1107, 991, 892 cm^{-1}. Anal. Calcd. for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19; F, 27.58; N, 3.39. Found: C, 43.65; H, 2.21; N, 3.37.



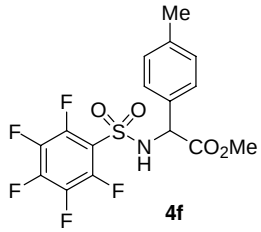
4d

Methyl 2-(4-chlorophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4d). Methyl 2-amino-2-(4-chlorophenyl)acetate hydrochloride, 2.36 g. **4d** (3.35 g, 78%); FCC - AcOEt/hexane (1 : 9), pasty wax. ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 7.19-7.16 (m, 2H), 6.23 (d, 1H, *J* = 7.2 Hz), 5.25 (d, 1H, *J* = 7.2 Hz), 3.72 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.0 (m, 1F), -159.2 (m, 2F). IR (nujol) 3268, 1738, 1634, 1509, 1294, 1160, 1100, 990 cm^{-1}. Anal. Calcd. for $C_{15}H_9ClF_5NO_4S$: C, 41.92; H, 2.11; N, 3.26. Found: C, 42.00; H, 2.08; N, 3.21.



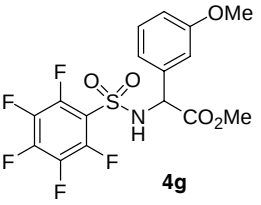
4e

Methyl 2-(4-bromophenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4e). Methyl 2-amino-2-(4-bromophenyl)acetate hydrochloride, 2.81 g. **4e** (3.89 g, 82%); FCC - AcOEt/hexane (1 : 9), white solid, mp 110-111°C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 2H), 7.13-7.10 (m, 2H), 6.33 (d, 1H, *J* = 7.3 Hz), 5.24 (d, 1H, *J* = 7.3 Hz), 3.72 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -146.0 (m, 1F), -159.2 (m, 2F). IR (nujol) 3271, 1748, 1522, 1363, 1286, 1253, 1180, 1110, 989, 617 cm^{-1}. Anal. Calcd. for $C_{15}H_9BrF_5NO_4S$: C, 37.99; H, 1.91; N, 2.95. Found: C, 38.03; H, 1.94; N, 2.95.



4f

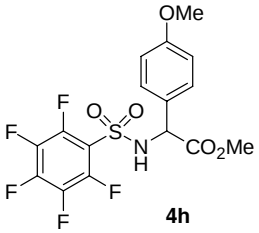
Methyl 2-(2,3,4,5,6-pentafluorophenylsulfonamido)-2-*p*-tolylacetate (4f). Methyl 2-amino-2-*p*-tolylacetate hydrochloride, 2.16 g. **4f** (3.68 g, 90%); FCC - AcOEt/hexane (1 : 9), white solid, mp 115,5-116,5 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10-7.07 (m, 2H), 7.03-7.01 (m, 2H), 6.40 (d, 1H, *J* = 7.2 Hz), 5.24 (d, 1H, *J* = 7.2 Hz), 3.71 (s, 3H), 2.26 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.4 (m, 2F), -147.7 (m, 1F), -160.2 (m, 2F). ^{13}C NMR (75 MHZ, $CDCl_3$) δ 169.8, 144.1 (dm, *J* = 255.5 Hz), 143.8 (dm, *J* = 255.6 Hz), 139.4, 137.3 (dm, *J* = 265.4 Hz), 130.7, 129.4, 127.3, 116.9, 59.7, 53.3, 20.8. IR (nujol) 3251, 1744, 1643, 1519, 1298, 1210, 1176, 1099, 992, 897 cm^{-1}. Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N, 3.42. Found: C, 46.99; H, 3.00; N, 3.38.



4g

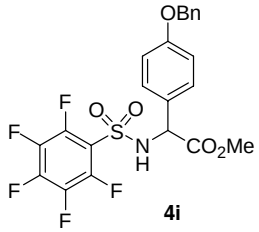
Methyl 2-(3-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4g). Methyl 2-amino-2-(3-methoxyphenyl)acetate hydrochloride, 2.32 g. **4g** (3.61 g, 85%); FCC - AcOEt/hexane (1 : 9), white solid, mp 88-89 °C. ^1H NMR (300 MHZ, $CDCl_3$) δ 7.16-7.11 (m, 1H), 6.79-6.70 (m, 3H), 6.56 (d, 1H, *J* = 7.7 Hz), 5.23 (d, 1H, *J* = 7.7 Hz), 3.72 (s, 3H), 3.71 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.2 (m, 1F), -160.2 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 159.9, 143.9 (dm, *J* = 256.5 Hz), 143.5 (dm, *J* = 259.5 Hz), 137.4 (dm, *J* = 251.2 Hz), 135.1, 130.1, 119.5, 116.9 (t, *J* = 12.0 Hz), 114.4, 112.8, 59.9, 55.1, 53.3. IR (nujol) 3295, 3244, 1740, 1729,

1644, 1520, 1311, 1179, 1101, 995, 891 cm^{-1}. Anal. Calcd. for $C_{16}H_{12}F_5NO_5S$: C, 45.18; H, 2.84; N, 3.29. Found: C, 45.23; H, 2.87; N, 3.25.



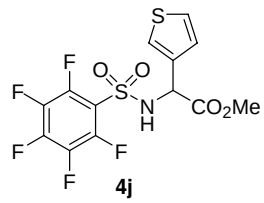
4h

Methyl 2-(4-methoxyphenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4h). Methyl 2-amino-2-(4-methoxyphenyl)acetate hydrochloride, 2.32 g. **4h** (3.40 g, 80%); FCC - AcOEt/hexane (1 : 9), white solid, mp 115-116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.10 (m, 2H), 6.74-6.71 (m, 2H), 6.27 (d, 1H, *J* = 7.5 Hz), 5.22 (d, 1H, *J* = 7.5 Hz), 3.74 (s, 3H), 3.71 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.2 (m, 1F), -160.0 (m, 2F). IR (nujol) 3263, 1748, 1610, 1518, 1303, 1174, 1091, 990 cm^{-1}. Anal. Calcd. for $C_{16}H_{12}F_5NO_5S$: C, 45.18; H, 2.84; N, 3.29. Found: C, 45.21; H, 2.89; N, 3.31.



4i

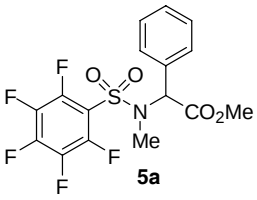
Methyl 2-(4-(benzyloxy)phenyl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4i). Methyl 2-amino-2-(4-(benzyloxy)phenyl)acetate hydrochloride, 3.08 g. **4i** (4.16 g, 83%); FCC - AcOEt/hexane (1 : 12), white solid, mp 103,5-104,5 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 7.13-7.10 (m, 2H), 6.83-6.79 (m, 2H), 6.20 (d, 1H, *J* = 7.1 Hz), 5.22 (d, 1H, *J* = 7.1 Hz), 4.97 (s, 2H), 3.71 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.5 (m, 2F), -147.0 (m, 1F), -159.8 (m, 2F). IR (nujol) 3275, 1741, 1627, 1518, 1310, 1176, 1100, 996, 884 cm^{-1}. Anal. Calcd. for $C_{22}H_{16}F_5NO_5S$: C, 52.70; H, 3.22; N, 2.79. Found: C, 52.74; H, 3.19; N, 2.83.



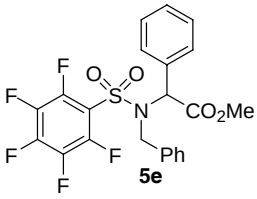
4j

Methyl 2-(thiophen-3-yl)-2-(2,3,4,5,6-pentafluorophenylsulfonamido)acetate (4j). Following the General Procedure, using 208 mg (1 mmol) of methyl 2-amino-2-(thiophen-3-yl)acetate hydrochloride and proportional amounts of the other reactives and solvents. **4j** (301 mg, 75%); FCC - AcOEt/hexane (1 : 9), white solid, mp 150-151 °C. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.26 (d, 1H, *J* = 3.0 Hz), 7.20 (dd, 1H, *J* = 5.0, 3.0 Hz), 6.89 (dd, 1H, *J* = 5.0, 0.9 Hz), 6.17 (d, 1H, *J* = 7.8 Hz), 5.41 (d, 1H, *J* = 7.8 Hz), 3.74 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -136.6 (m, 2F), -146.5 (m, 1F), -159.5 (m, 2F). IR (nujol) 3288, 1729, 1615, 1530, 1340, 1165, 982, 895 cm^{-1}. Anal. Calcd. for $C_{13}H_8F_5NO_4S_2$: C, 38.91; H, 2.01; N, 3.49. Found: C, 38.96; H, 2.07; N, 3.44.

SL-PTC *N*-Alkylation of Sulfonamide 4a: Synthesis of 5a,e

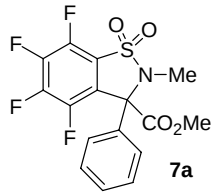


Methyl 2-(*N*-methyl-2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (5a). To a solution of sulfonamide **4a** (395 mg, 1 mmol) and TEBA (23 mg, 0.1 mmol) in dry MeCN (2 mL) at 25 °C, anhydrous K_2CO_3 (276 mg, 2 mmol) was added. This suspension was stirred for 10 min, then a solution of MeI (213 mg, 1.5 mmol) in MeCN (1 mL) was added under vigorous stirring, and the reaction was monitored by TLC (AcOEt : hexane – 1 : 9) until completion (24 h). The mixture was then diluted with AcOEt (5 mL), washed with brine (2 × 2 mL), dried over $MgSO_4$ and filtered. The solvent was removed under vacuum, the crude was purified by FCC – AcOEt/hexane (1 : 15), and sulphonamide **5a** (368 mg, 90%) was isolated as white solid, mp 67-69 °C (EtOH/water – 9 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.23 (m, 5H), 6.04 (s, 1H), 3.72 (s, 3H), 2.84 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 2F), -146.4 (m, 1F), -159.7 (m, 2F). IR (nujol) 1744, 1644, 1541, 1296, 1271, 1222, 1173, 1098, 1025, 699, 678. Anal. Calcd. for $C_{16}H_{12}F_5NO_4S$: C, 46.95; H, 2.95; N, 3.42. Found: C, 47.02; H, 3.00; N, 3.37. 3331.



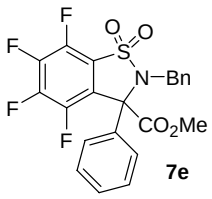
Methyl 2-(*N*-benzyl-2,3,4,5,6-pentafluorophenylsulfonamido)-2-phenylacetate (5e). Analogous preparation to that of **5a**, using $PhCH_2Br$ (188 mg, 1.1 mmol) as alkylating agent. The reaction mixture was stirred at 25 °C for 20 h; TLC - AcOEt/hexane (1 : 9). FCC - AcOEt/hexane (1 : 12). **5e** (427 mg, 88%); white solid, mp 106-108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 7.05-6.95 (m, 5H), 6.17 (s, 1H), 4.80 (d, 1H, J = 15.4 Hz), 4.25 (d, 1H, J = 15.4 Hz), 3.79 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 2F), -147.0 (m, 1F), -160.2 (m, 2F). IR (nujol), 1744, 1530, 1351, 1292, 1240, 1106, 669 cm^{-1}. Anal. Calcd. for $C_{22}H_{16}F_5NO_4S$: C, 54.43; H, 3.32; N, 2.89. Found: C, 54.48; H, 3.35; N, 2.92.

SL-PTC Ring Closing Reactions of *N*-Alkylsulfonamides 5a,e



7a

Methyl 4,5,6,7-tetrafluoro-1-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7a) by SL-PTC cyclization of *N*-methylsulfonamide 5a (Tab. 1). To a solution of *N*-methyl-sulfonamide **5a** (82 mg, 0.2 mmol) and TEBA (5 mg, 0.02 mmol) in dry DMSO (1 mL) at 25 °C, anhydrous Cs_2CO_3 (130 mg, 0.4 mmol) was added. This suspension was vigorously stirred for 15 min, monitoring by TLC (AcOEt : hexane – 1 : 9), then diluted with water (2 mL), extracted with DCM (3×10 mL). The solvent was removed under vacuum (RV). The residue was diluted with AcOEt (10 mL), washed with brine (5×2mL), dried over Mg_2SO_4 filtered and, after evaporation of the solvent (RV), purified by MPLC (AcOEt : hexane – 1 : 12) to give **7a** (142 mg, 91%) as a white solid, mp 165-166°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.40 (m, 3H), 7.26-7.23 (m, 2H), 3.91 (s, 3H), 2.84 (s, 3H). ^{19}F NMR (282, MHz, $CDCl_3$) δ -135 (m, 1F), -140.3 (m, 1F), -145.3 (m, 1F), -149 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 144.3 (dt, *J* = 261.6, 13.8 Hz), 143.4 (ddd, *J* = 261.6, 12.6, 3.8 Hz), 141.5 (dt, *J* = 261.6, 13.8 Hz), 141.0 (dd, *J* = 262.8, 13.8 Hz), 132.7, 129.9, 129.2, 127.4, 122.3 (dd, *J* = 13.4, 3.5 Hz), 118.2 (dd, *J* = 17.5, 3.1 Hz), 71.8, 53.8, 25.4. IR (nujol) 1748, 1638, 1516, 1495, 1296, 1256, 1230, 1170, 1077, 977, 916, 880, 693, 629, 614 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.31; H, 2.81; N, 3.64. HRMS (ESI positive) Calcd. for $C_{16}H_{11}F_4NNaO_4S$ $[M+Na]^+$: 412.02371. Found: 412.02401.

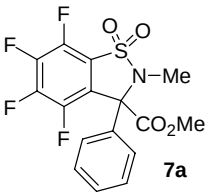


7e

Methyl 4,5,6,7-tetrafluoro-1-benzyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7e) by SL-PTC cyclization of *N*-benzylsulfonamide 5e. Analogous preparation to that of **7a**, using *N*-benzyl-sulfonamide **5e** (97 mg, 0.2 mmol). The reaction mixture was vigorously stirred for 20 h, monitoring by TLC (AcOEt : hexane – 1 : 7). After usual work-up, the crude was purified by MPLC (AcOEt : hexane – 1 : 12) and **7e** was isolated (42 mg, 45%) as a white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.31 (m, 5H), 7.25-7.20 (m, 5H), 4.70 (d, 1H, *J* = 16.1 Hz), 4.35 (d, 1H, *J* = 16.1 Hz), 3.60 (s, 3H). ^{19}F NMR (282 MHZ, $CDCl_3$): δ -135.2 (m, 1F), -140.1 (m, 1F), -144.9 (m, 1F), -148.9 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 144.4 (dt, *J* = 262.2, 15.2 Hz), 143.1 (dd, *J* = 259.9, 12.2 Hz), 141.5 (dm, *J* = 262.3 Hz), 141.2 (dm, *J* = 259.8 Hz), 135.2, 133.1, 129.7, 129.0, 128.2, 128.0, 127.8, 127.6, 122.3 (d, *J* = 13.9 Hz), 118.1 (d, *J* = 15.2 Hz), 72.5, 53.5, 45.3. IR (nujol) 1747, 1642, 1512, 1504, 1330, 1254, 1174, 1076, 996, 980, 914, 881, 829, 698, 607 cm^{-1}. Anal. Calcd. for $C_{22}H_{15}F_4NO_4S$: C, 56.77; H, 3.25; N, 3.01. Found: C, 56.81; H, 3.20; N, 3.06.

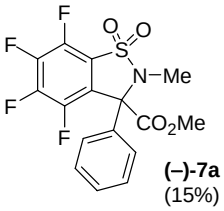
SL-PTC 'One-Pot' Synthesis of *N*-Alkyl-benzo[d]sultams 7a-f: General Procedure (Tab. 3)

To a solution of sulfonamide **4a** (395 mg, 1 mmol) and TEBA (23 mg, 0.1 mmol) in dry solvent (5 mL) at 25 °C, anhydrous alkaline metal carbonate (2-4 mmol) was added. The resulting heterogeneous mixture was stirred for 10 min, then the alkylating agent RX (1.5 mmol) was added and the reaction was monitored by TLC (AcOEt : hexane – 1 : 6) until completion. The mixture was diluted with water and extracted with DCM and concentrated; the residue was diluted with AcOEt (10 mL) and washed with brine (5×10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent (RV), the crude was purified by MPLC (AcOEt : hexane – 1 : 9). Starting alkylating agent (RX), dry solvent, anhydrous base, reaction time, product, yield, physical and analytical data are as follows.



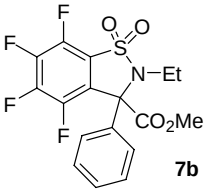
7a

Methyl 4,5,6,7-tetrafluoro-1-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7a). MeI, 213 mg; DMSO; Cs_2CO_3 (652 mg, 2 mmol); 1.25 h. **7a** (366 mg, 94%), white solid, mp 166°C. NMR data match those reported before (page S-8).



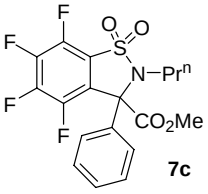
(–)-7a (15%)

(–)-Methyl 4,5,6,7-tetrafluoro-1-methyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7a). Analogous preparation to that of **7a**, starting from ***S*-4a** methyl ester hydrochloride. White solid, mp 164 °C; $[\alpha]_D^{20}$ -10.2 (*c* 1, $CHCl_3$). NMR spectra match those of **7a**. (see page S-59 for chiral HPLC analysis).



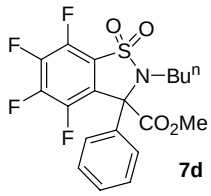
7b

Methyl 4,5,6,7-tetrafluoro-1-ethyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7b). EtI, 234 mg; DMSO; K_2CO_3 (276 mg, 2 mmol); 20 h. **7b** (334 mg, 83%), white solid, mp 109.5-110.5°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 3H), 7.30-7.26 (m, 2H), 3.91 (s, 3H), 3.47-3.27 (m, 2H), 1.21 (t, 3H, *J* = 7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.3 (m, 1F), -140.5 (m, 1F), -145.3 (m, 1F), -149 (m, 1F). IR (nujol) 1749, 1642, 1511, 1495, 1298, 1268, 1182, 1161, 1079, 942, 727, 699, 636, 603 cm^{-1}. Anal. Calcd. for $C_{17}H_{13}F_4NO_4S$: C, 50.62; H, 3.25; N, 3.47. Found: C, 50.59; H, 3.29; N, 3.43.



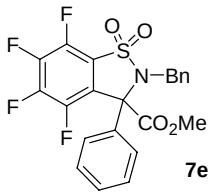
7c

Methyl 4,5,6,7-tetrafluoro-1-propyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7c). *n*-PrI, 255 mg; DMSO; Cs_2CO_3 (1.30 g, 4 mmol); 16 h. **7c** (209 mg, 50%), white solid, mp 56-57°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 3.90 (s, 3H), 3.34-3.10 (m, 2H), 1.71-1.56 (m, 2H), 0.79 (t, 3H, *J* = 7.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.4 (m, 1F), -140.5 (m, 1F), -145.3 (m, 1F), -149.1 (m, 1F). IR (nujol) 1748, 1639, 1510, 1497, 1300, 1232, 1209, 1167, 1078, 993, 876, 699 cm^{-1}. Anal. Calcd. for $C_{18}H_{15}F_4NO_4S$: C, 51.80; H, 3.62; N, 3.36. Found: C, 51.75; H, 3.60; N, 3.41.



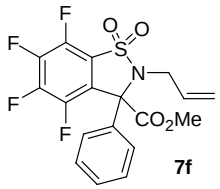
7d

Methyl 4,5,6,7-tetrafluoro-1-butyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7d). *n*-BuI, 276 mg; NMP; K_2CO_3 (276 mg, 2 mmol); 20 h. **7d** (267 mg, 62%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 3H), 7.29-7.27 (m, 2H), 3.89 (s, 3H), 3.89-3.14 (m, 2H), 1.63-1.55 (m, 2H), 1.27-1.15 (m, 2H), 0.80 (t, 3H, *J* = 7.35 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.4 (m, 1F), -140.6 (m, 1F), -145.4 (m, 1F), -149.2 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 144.3 (dt, *J* = 262.3, 14.8 Hz), 143.5 (dd, *J* = 260.5, 11.5 Hz), 141.5 (dt, *J* = 261.7, 14.1 Hz), 141.1 (dd, *J* = 261.7, 12.5 Hz), 134.1, 130.1, 129.5, 128.0, 122.7 (d, *J* = 13.3 Hz), 118.9 (d, *J* = 18 Hz), 72.8, 54.2, 43.3, 31.5, 20.4, 13.8. IR (nujol) 1744, 1633, 1510, 1488, 1290, 1248, 1239, 1170, 1077, 977, 910, 880, 693 cm^{-1}. Anal. Calcd. for $C_{19}H_{17}F_4NO_4S$: C, 52.90; H, 3.97; N, 3.25. Found: C, 52.96; H, 4.00; N, 3.20.



7e

Methyl 4,5,6,7-tetrafluoro-1-benzyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7e). BnBr, 257 mg; DMSO (50 °C); Na_2CO_3 (424 mg, 4 mmol); 20 h. **7e** (149 mg, 32%), white wax. NMR data match those reported in S-8. Anal. Calcd. for $C_{22}H_{15}F_4NO_4S$: C, 56.77; H, 3.25; N, 3.01. Found: C, 56.81; H, 3.28; N, 2.96.

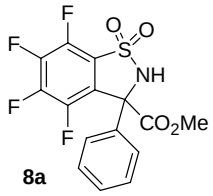


7f

Methyl 4,5,6,7-tetrafluoro-1-allyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (7f). Allyl bromide, 182 mg; MeCN (50 °C); Na_2CO_3 (424 mg, 4 mmol); 24 h. **7f** (191 mg, 46%), white solid; mp 111-112°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 3H), 7.31-7.27 (m, 2H), 5.88-5.75 (m, 1H), 5.20-5.08 (m, 2H), 4.03-3.78 (m, 2H), 3.89 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -135.2 (m, 1F), -140.5 (m, 1F), -145.2 (m, 1F), -149.1 (m, 1F). IR (nujol) 1748, 1643, 1516, 1498, 1302, 1262, 1230, 1171, 1077, 977, 916, 880, 691 cm^{-1}. Anal. Calcd. for $C_{18}H_{13}F_4NO_4S$: C, 52.05; H, 3.15; N, 3.37. Found: C, 52.00; H, 3.19; N, 3.34.

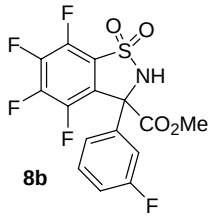
Synthesis of Benzo[d]sultams 8a-j: General Procedure (Tab. 6)

The solution of sulfonamide **4** (1 mmol) and DBU (609 mg, 4 mmol) in dry DME (5 mL), was stirred at 25 °C until completion (TLC control). The solution was then diluted with AcOEt (10 mL), washed with aqueous 5% citric acid (3×10 mL), saturated $NaHCO_3$ solution (2×10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure (RV), giving the sultam **8a-j**, without any further purification. Starting sulfonamide **4a-j**, reaction time, product, yield, physical and analytical data are as follows.



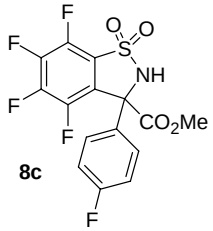
8a

Methyl 4,5,6,7-tetrafluoro-3-phenyl-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8a). In the case of the synthesis of compound **8a**, sulfonamide **4a** (3.95 g, 10 mmol), DBU (6.09 g, 40 mmol) and DME (50 mL) were used; 4 h. **8a** (3.60 g, 96%), white solid; mp 98-99°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 6.38 (s, 1H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.1 (m, 1F), -144 (m, 1F), -147.9 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 144.6 (dt, *J* = 262.2, 14.3 Hz), 143.6 (ddd, *J* = 261.8, 12.4, 3.3 Hz), 141.6 (dt, *J* = 262.1, 14.2 Hz), 140.9 (dd, *J* = 261.6, 12.5 Hz), 135.4, 129.6, 129.0, 126.2, 121.8 (d, *J* = 14.3 Hz), 119.6 (d, *J* = 17.8 Hz), 69.9, 54.3. IR (nujol) 3280, 1748, 1637, 1512, 1376, 1319, 1257, 1173, 1035, 914 cm^{-1}. Anal. Calcd. for $C_{15}H_9F_4NO_4S$: C, 48.01; H, 2.42; N, 3.73. Found: C, 47.96; H, 2.44; N, 3.73.



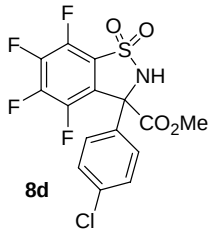
8b

Methyl 4,5,6,7-tetrafluoro-3-(3-fluorophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8b). 4b, 413 mg; 5 h. **8b** (373 mg, 95%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.33 (m, 1H), 7.19-7.06 (m, 3H), 6.4 (br, 1H), 3.94 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -110.9 (s, 1F), -132.5 (m, 1F), -139.7 (m, 1F), -143.5 (m, 1F), -147.3 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 162.8 (d, *J* = 247.7 Hz), 144.9 (dt, *J* = 262.8, 13.8 Hz), 143.7 (ddd, *J* = 260.4, 11.3, 2.5 Hz), 141.9 (dt, *J* = 262.8, 13.8 Hz), 141.1 (dd, *J* = 260.3, 11.3 Hz), 137.8, 130.9 (d, *J* = 7.5 Hz), 122.2, 121.3 (dd, *J* = 14.3, 3.1 Hz), 119.7 (dd, *J* = 18, 2.5 Hz), 116.9 (d, *J* = 20.1 Hz), 114.0 (d, *J* = 23.9 Hz), 69.4, 54.8. IR (nujol) 3275, 1752, 1631, 1508, 1376, 1324, 1263, 1175, 1031, 840 cm^{-1}. Anal. Calcd. for $C_{15}H_8F_5NO_4S$: C, 45.81; H, 2.05; N, 3.56. Found: C, 45.84; H, 2.09; N, 3.52.



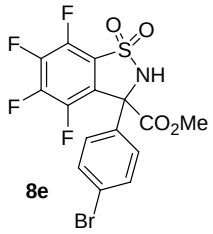
8c

Methyl 4,5,6,7-tetrafluoro-3-(4-fluorophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8c). 4c, 413 mg; 5 h. **8c** (385, 98%), white solid; mp 83.5-84.5°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.33 (m, 2H), 7.10-7.04 (m, 2H), 6.32 (s, 1H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -111.2 (s, 1F), -132.8 (m, 1F), -139.6 (m, 1F), -143.5 (m, 1F), -147.3 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 163.7 (d, *J* = 249.3Hz), 145.2 (dt, *J* = 261.1, 14.8 Hz), 144.0 (ddd, *J* = 258.3, 12.9, 2.9 Hz), 142.3 (dt, *J* = 261.1, 14.1 Hz), 141.6 (dd, *J* = 258.3, 12.4 Hz), 131.8, 129.0, 122.1 (d, *J* = 14.3 Hz), 120.1 (d, *J* = 17.2 Hz), 116.6 (d, *J* = 22.3 Hz), 69.8, 55.1. IR (nujol) 3272, 1750, 1635, 1508, 1376, 1321, 1261, 1175, 1038, 914, 843 cm^{-1}. Anal. Calcd. for $C_{15}H_8F_5NO_4S$: C, 45.81; H, 2.05; N, 3.56. Found: C, 45.82; H, 2.09; N, 3.60.



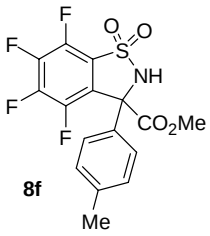
8d

Methyl 4,5,6,7-tetrafluoro-3-(4-chlorophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8d). 4d, 430 mg; 5 h. **8d** (365 mg, 91%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 6.26 (s, 1H), 3.94 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -139.5 (m, 1F), -143.4 (m, 1F), -147.1 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 144.9 (dt, *J* = 264.1, 15.1 Hz), 143.7 (ddd, *J* = 261.6, 12.6, 5.0 Hz), 141.9 (dt, *J* = 264.1, 15.1 Hz), 141.2 (dd, *J* = 261.6, 12.6 Hz), 136.1, 134.0, 129.4, 127.9, 121.4 (dd, *J* = 15.1, 3.8 Hz), 119.7 (dd, *J* = 17.6, 3.8 Hz), 69.4, 54.8. IR (nujol) 3284, 1739, 1648, 1507, 1379, 1325, 1270, 1185, 1028, 911 cm^{-1}. Anal. Calcd. for $C_{15}H_8ClF_4NO_4S$: C, 43.97; H, 1.97; N, 3.42. Found: C, 44.03; H, 2.00; N, 3.45.



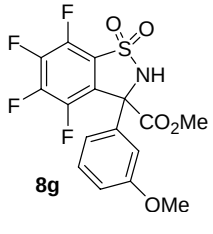
8e

Methyl 4,5,6,7-tetrafluoro-3-(4-bromophenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8e). 4e, 474 mg; 5 h. **8e** (422 mg, 93%), white solid; mp 49.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H), 7.27-7.24 (m, 2H), 5.93 (s, 1H), 3.93 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -139.6 (m, 1F), -143.5 (m, 1F), -147.2 (m, 1F). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 144.9 (dt, *J* = 262.8, 15.1 Hz), 143.7 (ddd, *J* = 261.6, 12.6, 3.8 Hz), 141.9 (dt, *J* = 262.8, 14.8 Hz), 141.1 (dd, *J* = 261.6, 12.6 Hz), 134.6, 132.3, 128.1, 124.1, 121.4 (dd, *J* = 14.6, 3.3 Hz), 119.7 (dd, *J* = 18.2, 2.9 Hz), 69.5, 54.8. IR (nujol) 3276, 1738, 1630, 1518, 1361, 1302, 1257, 1174, 1044, 906 cm^{-1}. Anal. Calcd. for $C_{15}H_8BrF_4NO_4S$: C, 39.67; H, 1.78; N, 3.08. Found: C, 39.61; H, 1.72; N, 3.13.



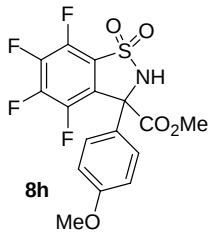
8f

Methyl 4,5,6,7-tetrafluoro-3-(4-methylphenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8f). 4f, 409 mg, 6 h. **8f** (385 mg, 99%),white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H), 6.32 (s, 1H), 3.93 (s, 3H), 2.34 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.4 (m, 1F), -140.1 (m, 1F), -144.0 (m, 1F), -147.9 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.6 (dt, *J* = 276.7, 15.8 Hz), 143.7 (dd, *J* = 261.9, 12.1 Hz), 141.6 (dm, *J* = 276.5 Hz), 141.1 (dd, *J* = 261.9, 12.8 Hz), 140.0, 132.5, 129.8, 126.2, 122.1 (d, *J* = 11.2 Hz), 119.8 (d, *J* = 15.4 Hz), 69.8, 54.4, 21.0. IR (nujol) 3238, 1720, 1509, 1391, 1355, 1324, 1294, 1189, 1169, 1061, 1039, 911 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}F_4NO_4S$: C, 49.36; H, 2.85; N, 3.60. Found: C, 49.32; H, 2.88; N, 3.62.



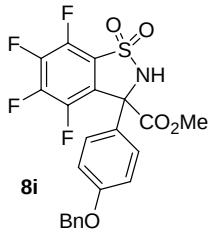
8g

Methyl 4,5,6,7-tetrafluoro-3-(3-methoxyphenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8g). 4g, 425 mg, 6 h. **8g** (397 mg, 98%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 1H), 6.93-6.90 (m, 3H), 6.32 (s, 1H), 3.93 (s, 3H), 3.76 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.0 (m, 1F), -140.1 (m, 1F), -143.9 (m, 1F), -147.8 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 160.0, 144.7 (dt, *J* = 261.7, 14.3 Hz), 143.8 (dd, *J* = 262.5, 12.1 Hz), 141.7 (dt, *J* = 261.6, 14.3 Hz), 141.1 (dd, *J* = 262.5, 12.0 Hz), 136.9, 130.2, 121.7 (d, *J* = 11.3 Hz), 119.7 (d, *J* = 14.2 Hz), 118.4, 114.7, 112.7, 69.8, 55.3, 54.5. IR (nujol) 3261, 1748, 1603, 1455, 1436, 1358, 1326, 1261, 1177, 1047, 909 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}F_4NO_5S$: C, 47.41; H, 2.74; N, 3.46. Found: C, 47.44; H, 2.77; N, 3.42.



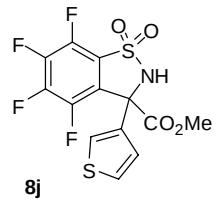
8h

Methyl 4,5,6,7-tetrafluoro-3-(4-methoxyphenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8h). 4h, 425 mg, 8 h. **8h** (385 mg, 95%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 2H), 6.88-6.85 (m, 2H), 5.9 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -132.7 (m, 1F), -140.2 (m, 1F), -144.1 (m, 1F), -148.1 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 160.5, 144.7 (dt, *J* = 264.2, 14.3 Hz), 143.7 (dd, *J* = 261.9, 12.1 Hz), 141.6 (dt, *J* = 264.2, 14.4 Hz), 140.9 (dd, *J* = 261.9, 12.1 Hz), 127.7, 127.2, 122.2 (*J* = 13.6 Hz), 119.8 (d, *J* = 17.4 Hz), 114.1, 69.7, 55.3, 54.4. IR (nujol) 3270, 1750, 1600, 1458, 1436, 1352, 1326, 1258, 1170, 1050, 912 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}F_4NO_5S$: C, 47.41; H, 2.74; N, 3.46. Found: C, 47.44; H, 2.77; N, 3.42.



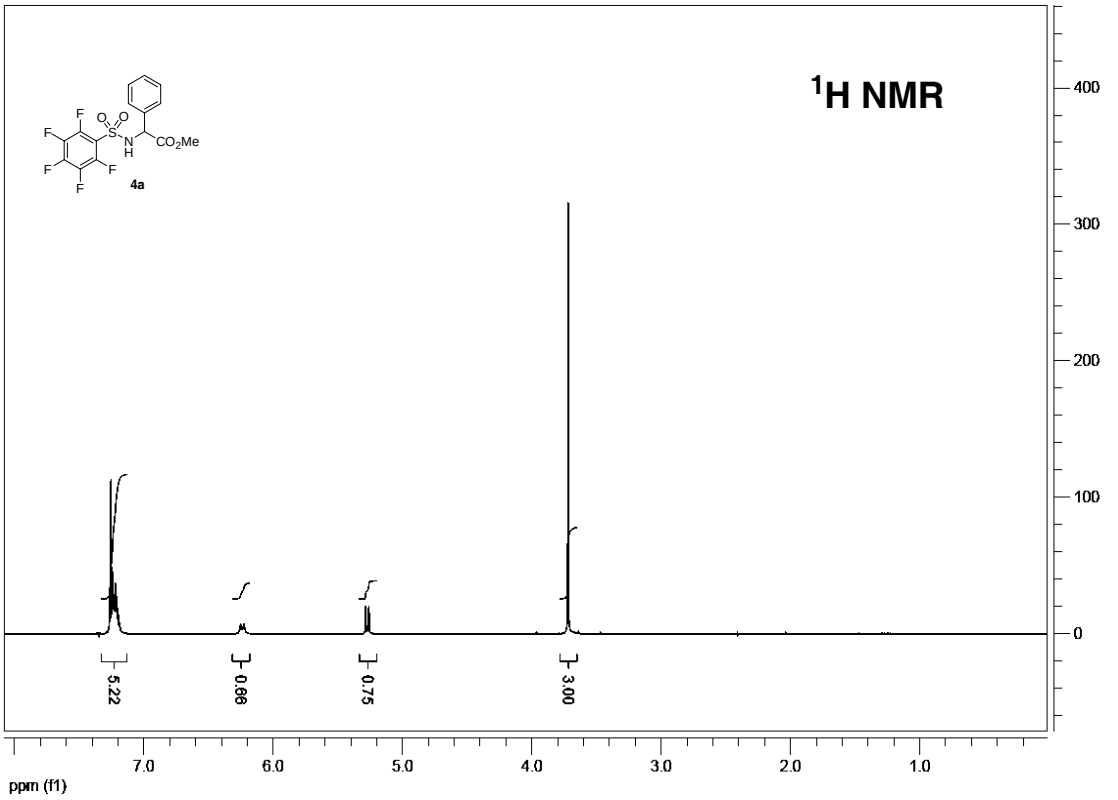
8i

Methyl 4,5,6,7-tetrafluoro-3-(4-benzyloxyphenyl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8i). 4i, 501 mg, 12 h. **8i** (390 mg, 81%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 7.31-7.25 (m, 2H), 7.00-6.96 (m, 2H), 6.13 (s, 1H), 5.06 (s, 1H), 3.93 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ -132.5 (m, 1F), -140.0 (m, 1F), -143.9 (m, 1F), -147.9 (m, 1F). IR (nujol) 3284, 1739, 1645, 1508, 1371, 1304, 1255, 1170, 1022, 906 cm^{-1}. Anal. Calcd. for $C_{22}H_{15}F_4NO_5S$: C, 54.89; H, 3.14; N, 2.91. Found: C, 54.92; H, 3.06; N, 2.88.



8j

Methyl 4,5,6,7-tetrafluoro-3-(thiophen-3-yl)-2,3-dihydrobenzo[d]isothiazole-3-carboxylate 1,1-dioxide (8j). Using 160 mg (0.4 mmol) of **4j**, 8 h. **8j** (134 mg, 88%), white wax. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, 1H, *J* = 3.5 Hz), 7.34 (dd, 1H, *J* = 5.2, 3.5 Hz), 7.12 (d, 1H, *J* = 5.2 Hz), 5.3 (s, 1H), 3.92 (s, 3H).^{19}F NMR (282 MHz, $CDCl_3$) δ -133.2 (m, 1F), -139.7 (m, 1F), -143.8 (m, 1F), -147.8 (m, 1F). δ 167.8, 146. (dt, *J* = 264.8, 13.9 Hz), 143.6 (dd, *J* = 261.5, 11.5 Hz), 141.7 (dt, *J* = 264.7, 13.9 Hz), 141.0 (dd, *J* = 261.4, 11.6 Hz), 135.8, 127.5, 125.8, 124.9, 122.1, 119.3, 66.9, 54.7. IR (nujol) 3280, 1753, 1639, 1499, 1378, 1318, 1248, 1172, 1032, 912, 840 cm^{-1}. Anal. Calcd. for $C_{13}H_7F_4NO_4S_2$: C, 40.95; H, 1.85; N, 3.67. Found: C, 40.99; H, 1.88; N, 3.70.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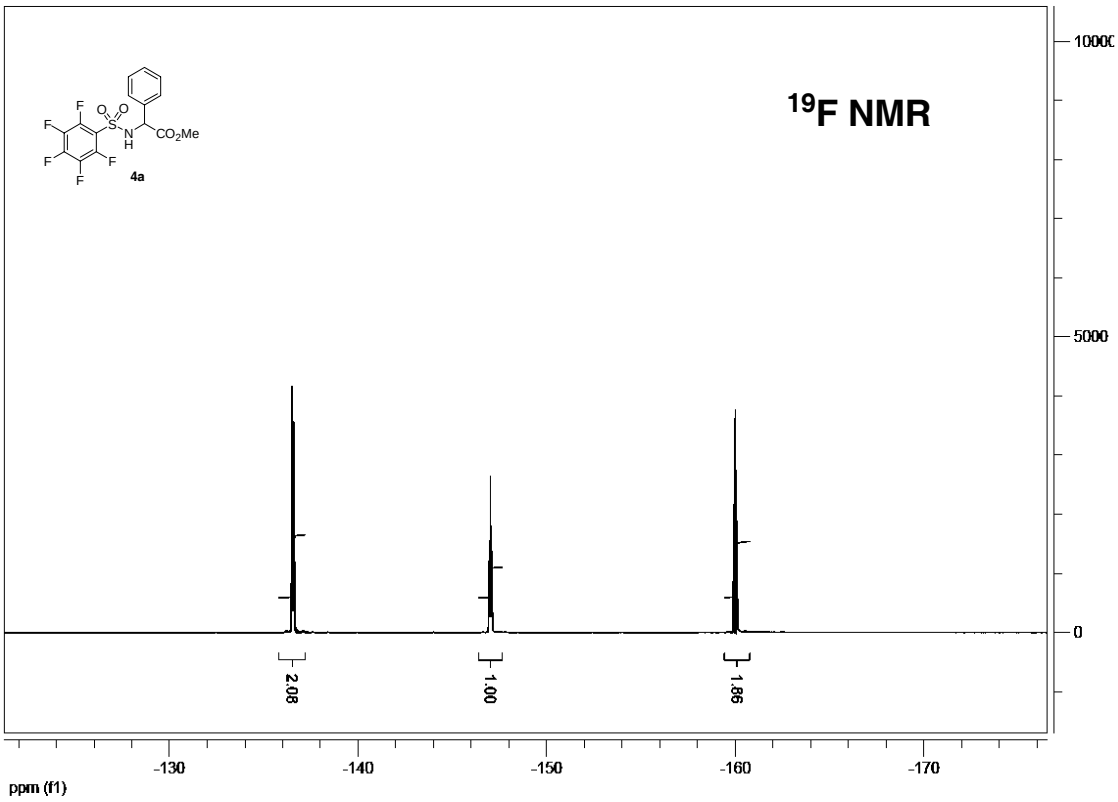
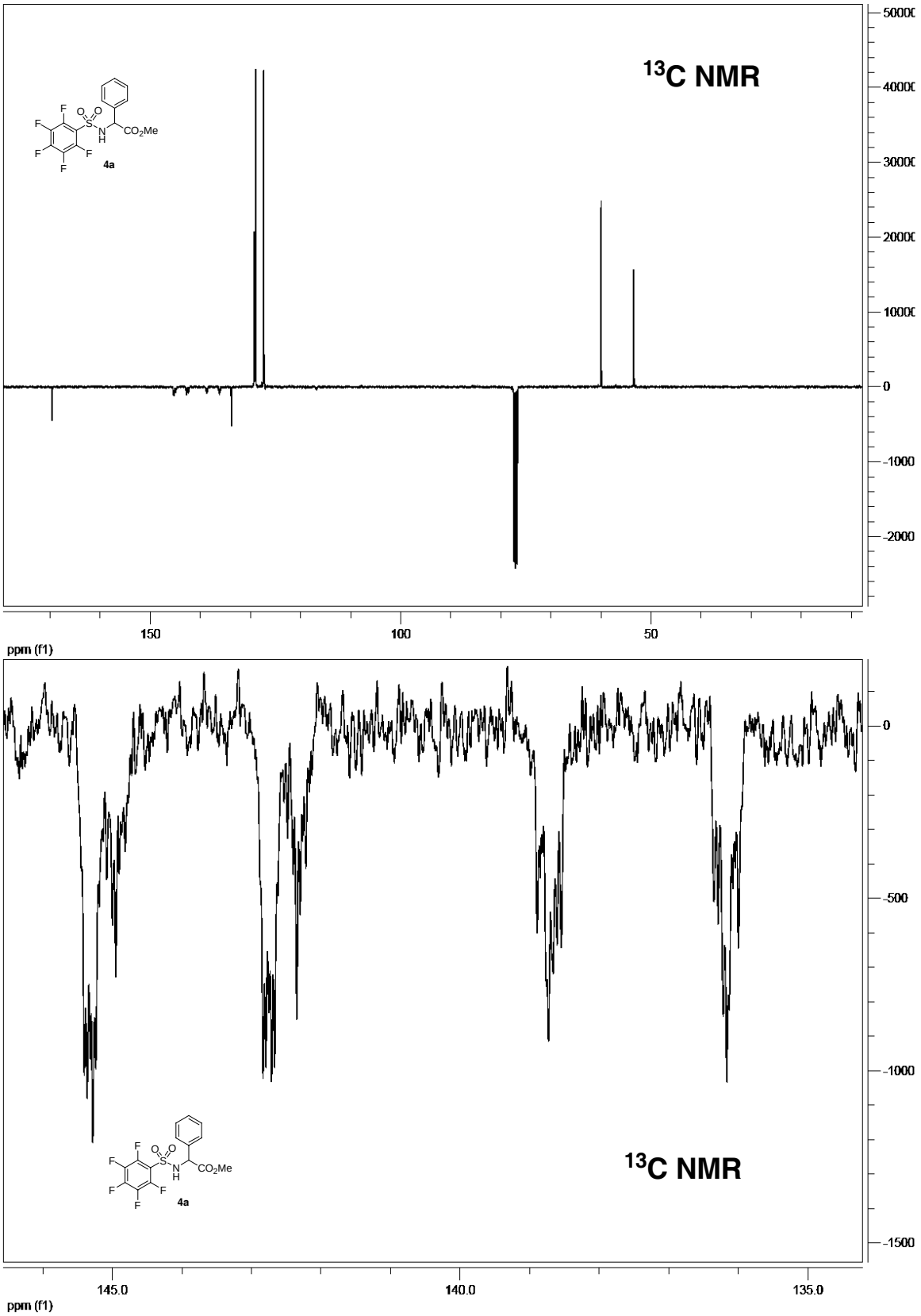
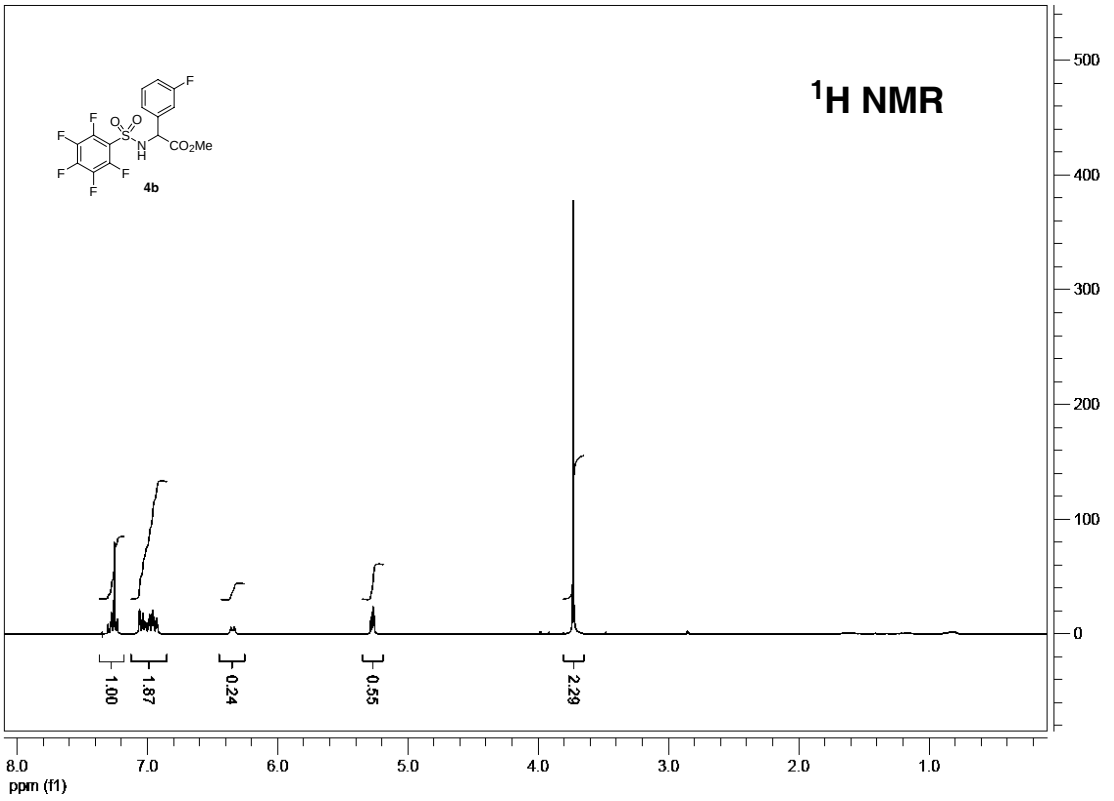
4a
5.22
0.66
0.75
3.00
ppm (f1)


^{19}F NMR
4a
2.08
1.00
1.86
ppm (f1)


^{13}C NMR
4a
50000
40000
30000
20000
10000
0
-1000
-2000
150
100
50
ppm (f1)
0
-500
-1000
-1500
^{13}C NMR
4a
145.0
140.0
135.0
ppm (f1)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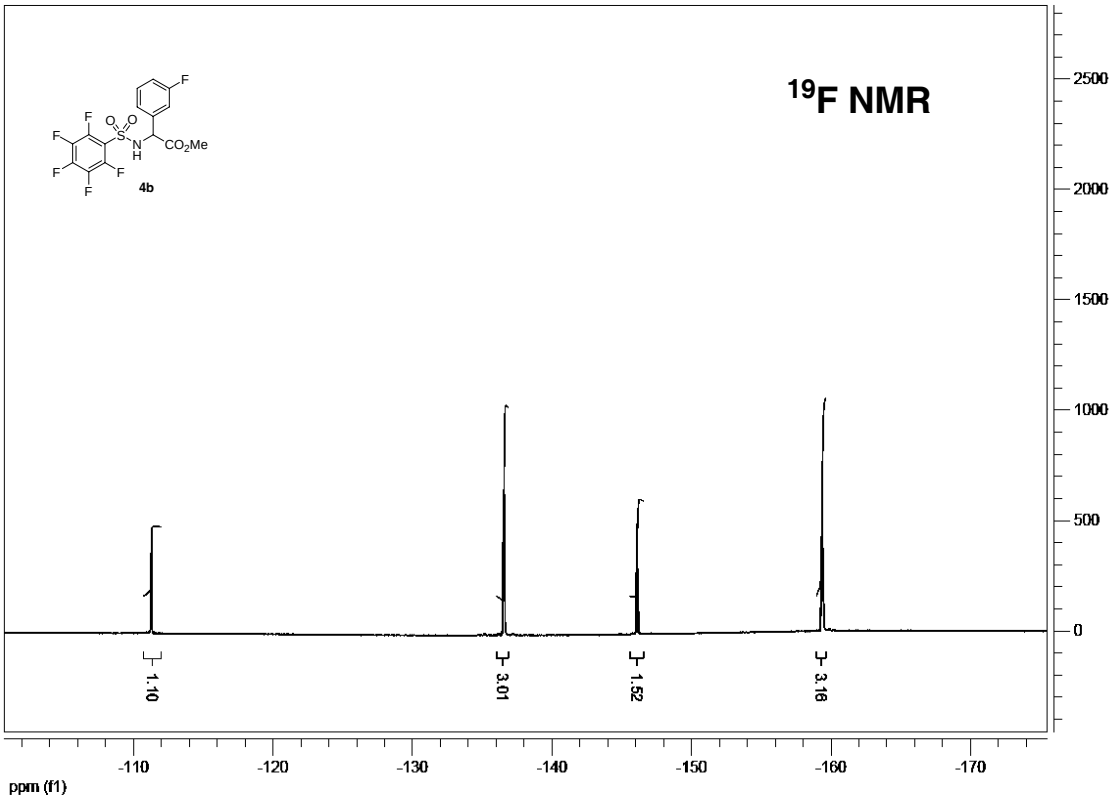
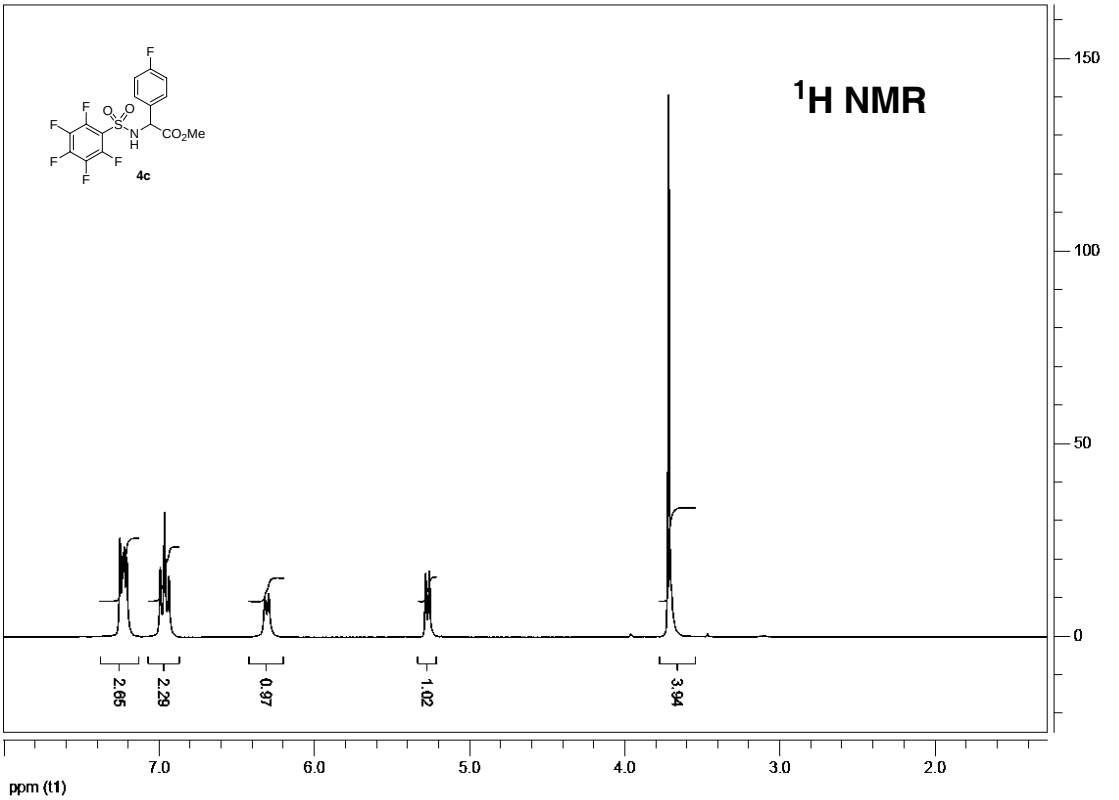
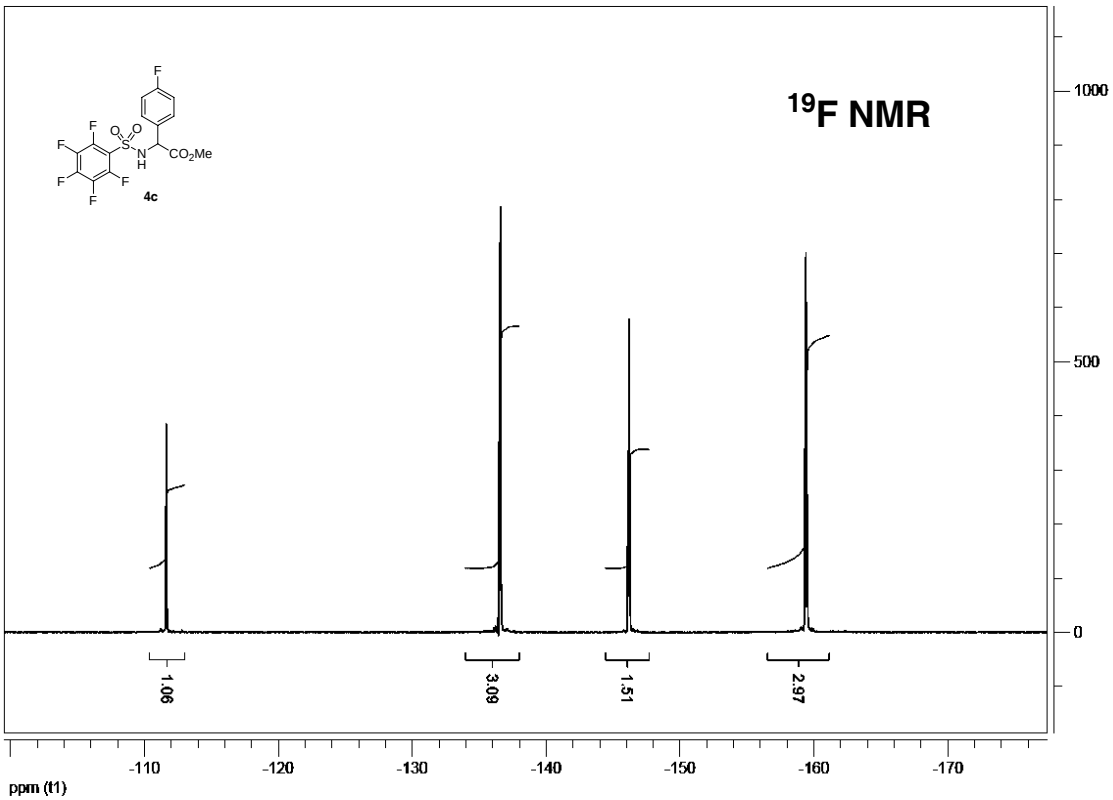
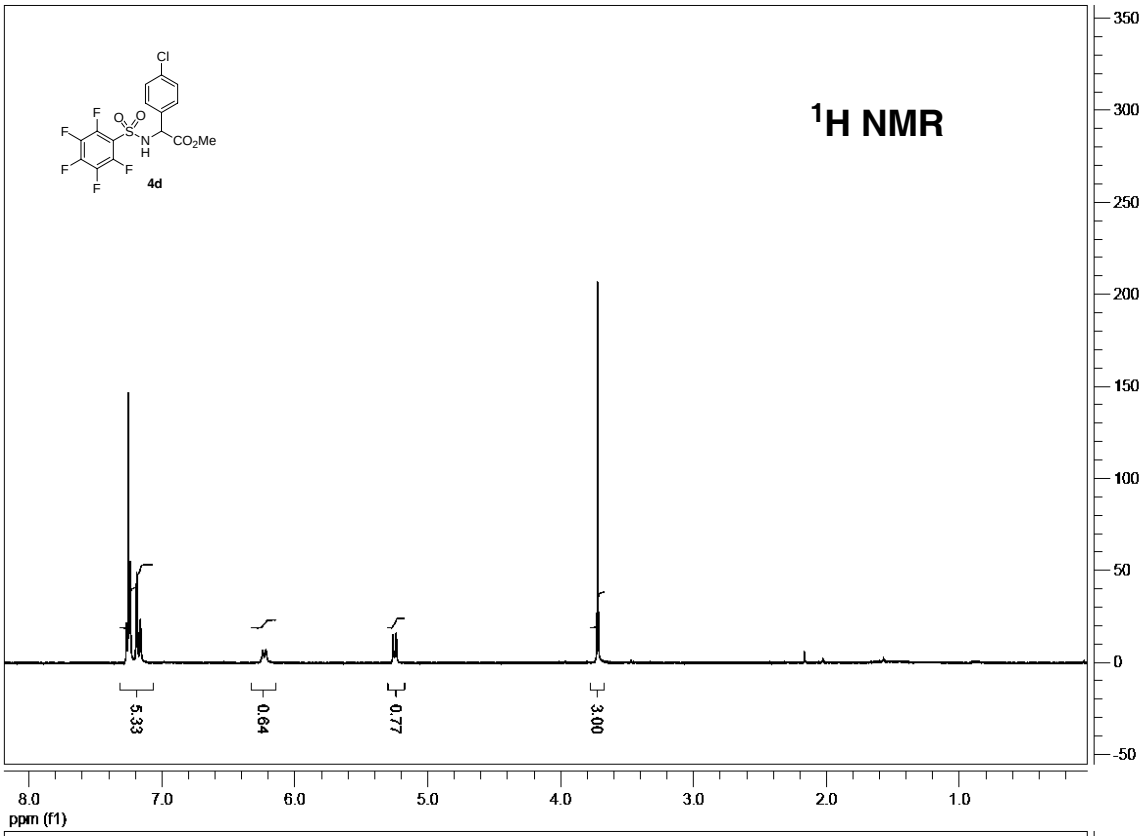
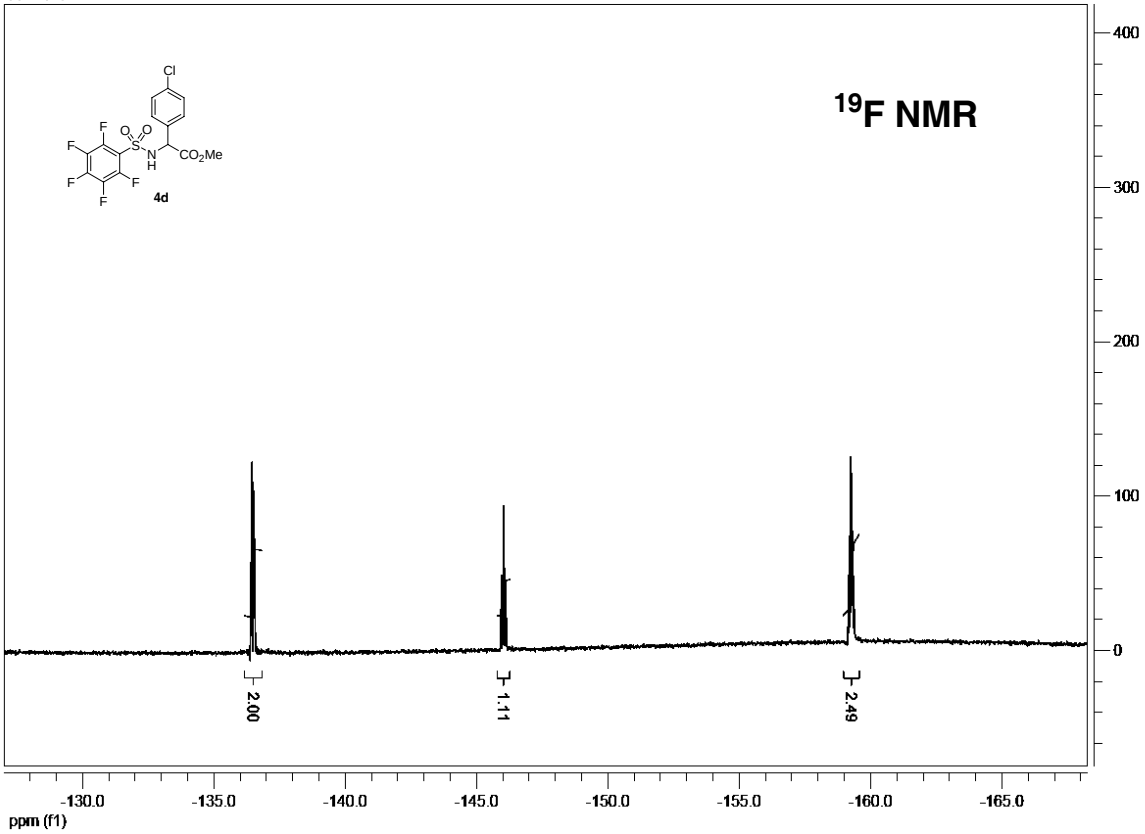
4b
1.00
1.87
0.24
0.55
2.29
ppm (f1)

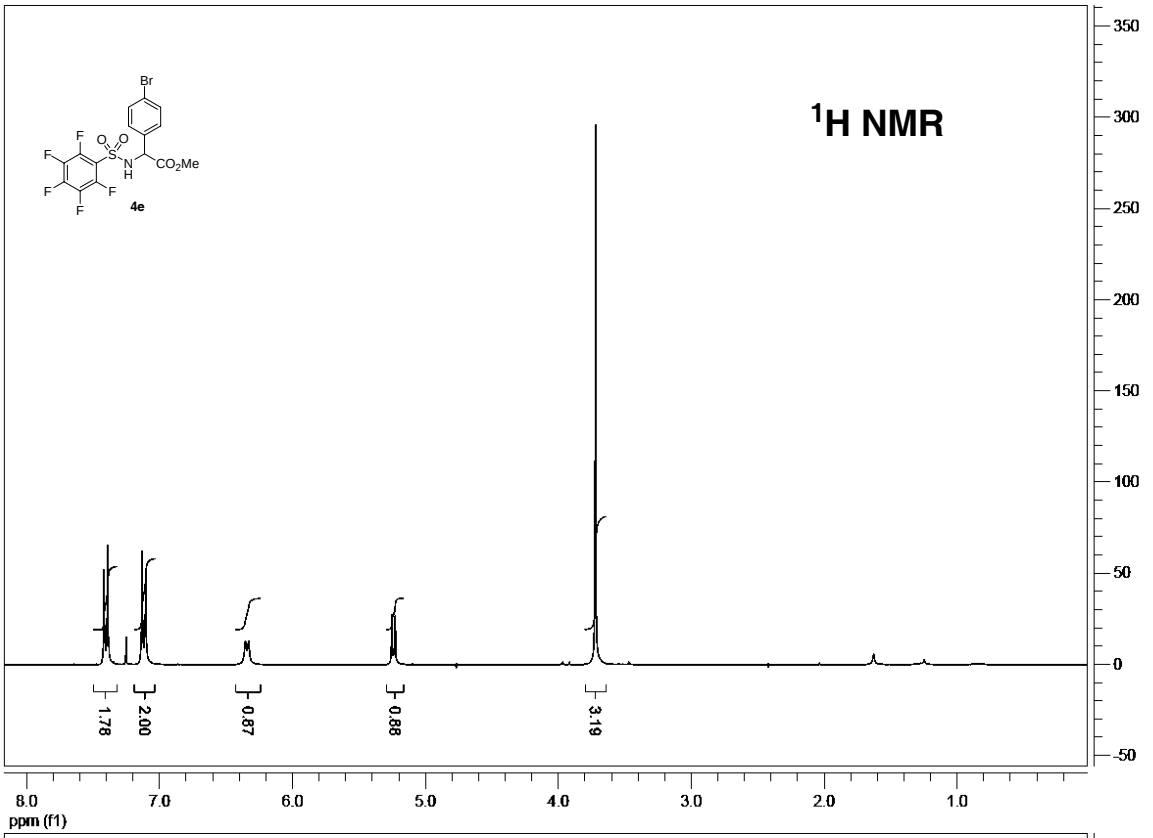

^{19}F NMR
4b
1.10
3.01
1.52
3.16
ppm (f1)

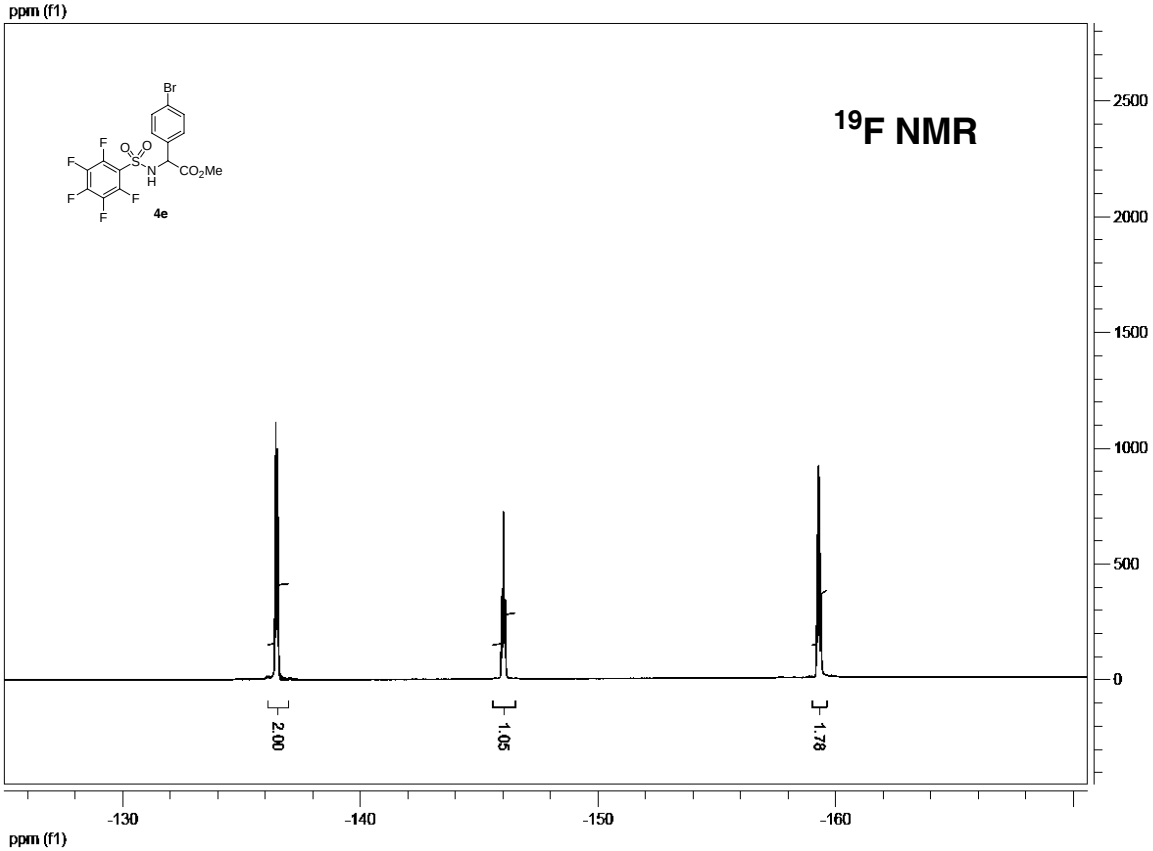

4c
^{1}H NMR
150
100
50
0
2.65
2.29
0.97
1.02
3.94
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

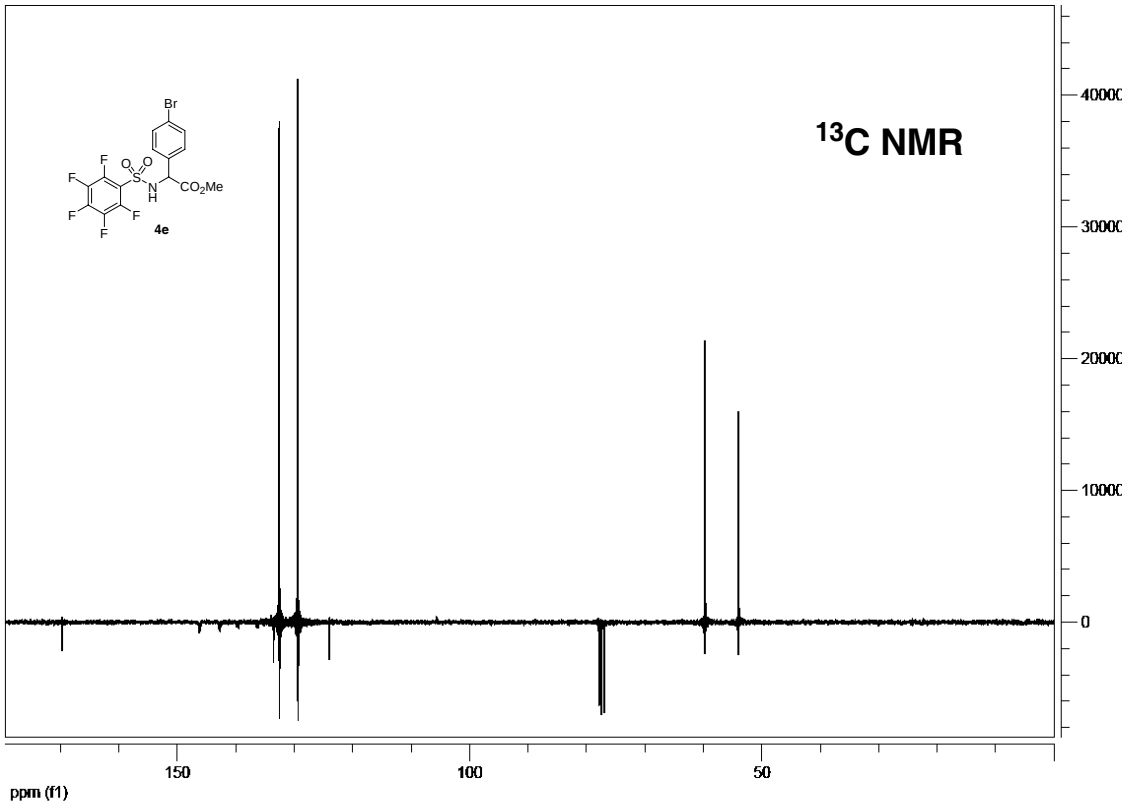

4c
^{19}F NMR
1000
500
0
1.06
3.09
1.51
2.97
-110
-120
-130
-140
-150
-160
-170
ppm (t1)

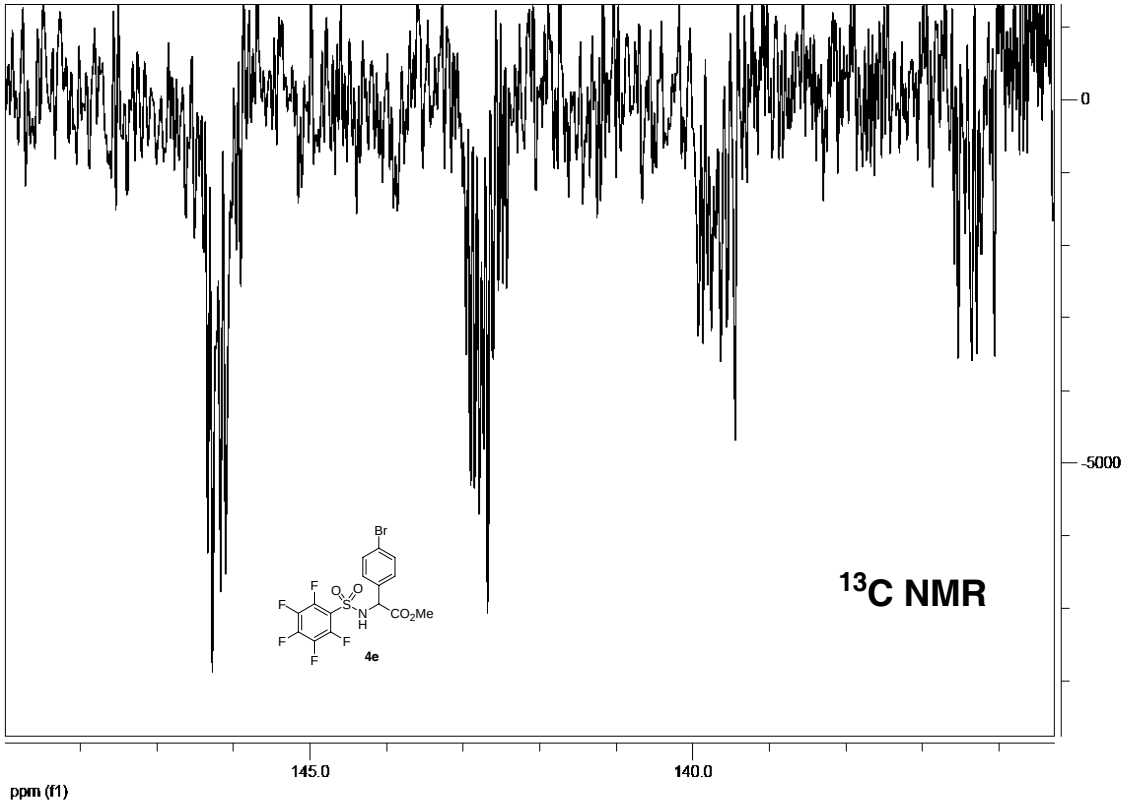

^{1}H NMR
4d
5.33
0.64
0.77
3.00
ppm (f1)

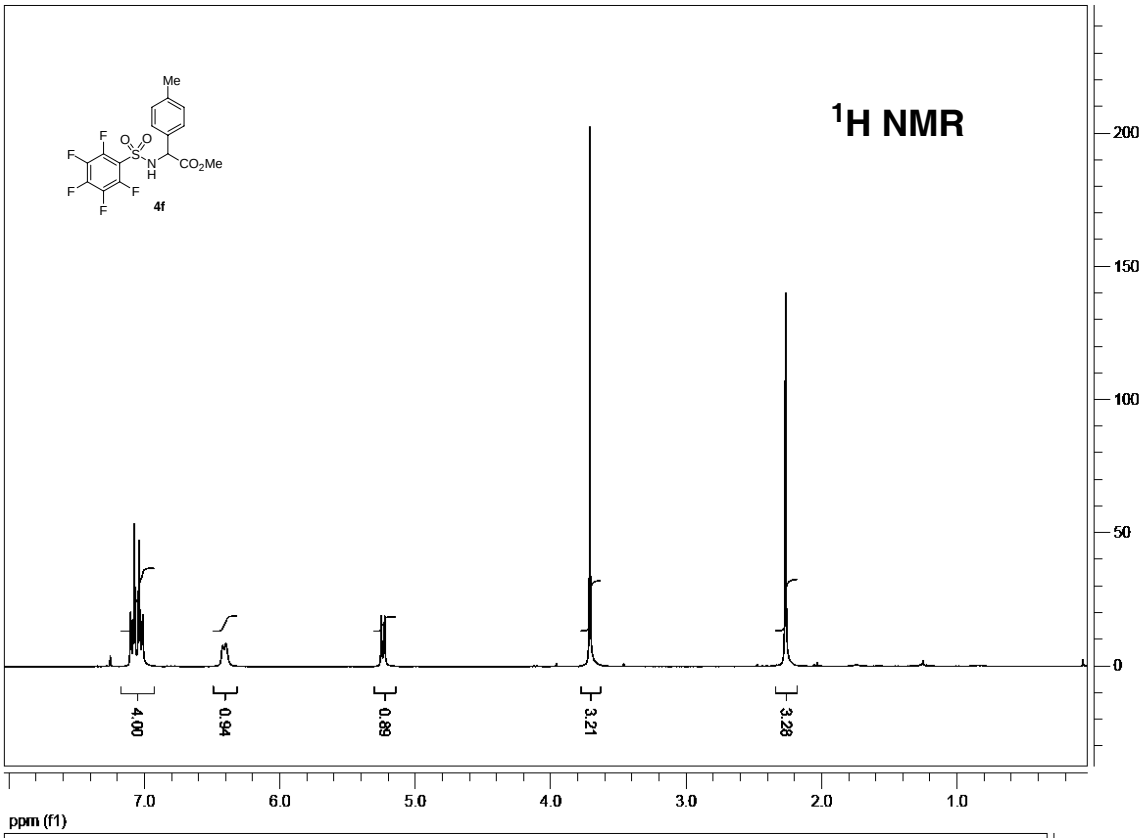

^{19}F NMR
4d
2.00
1.11
2.49
ppm (f1)

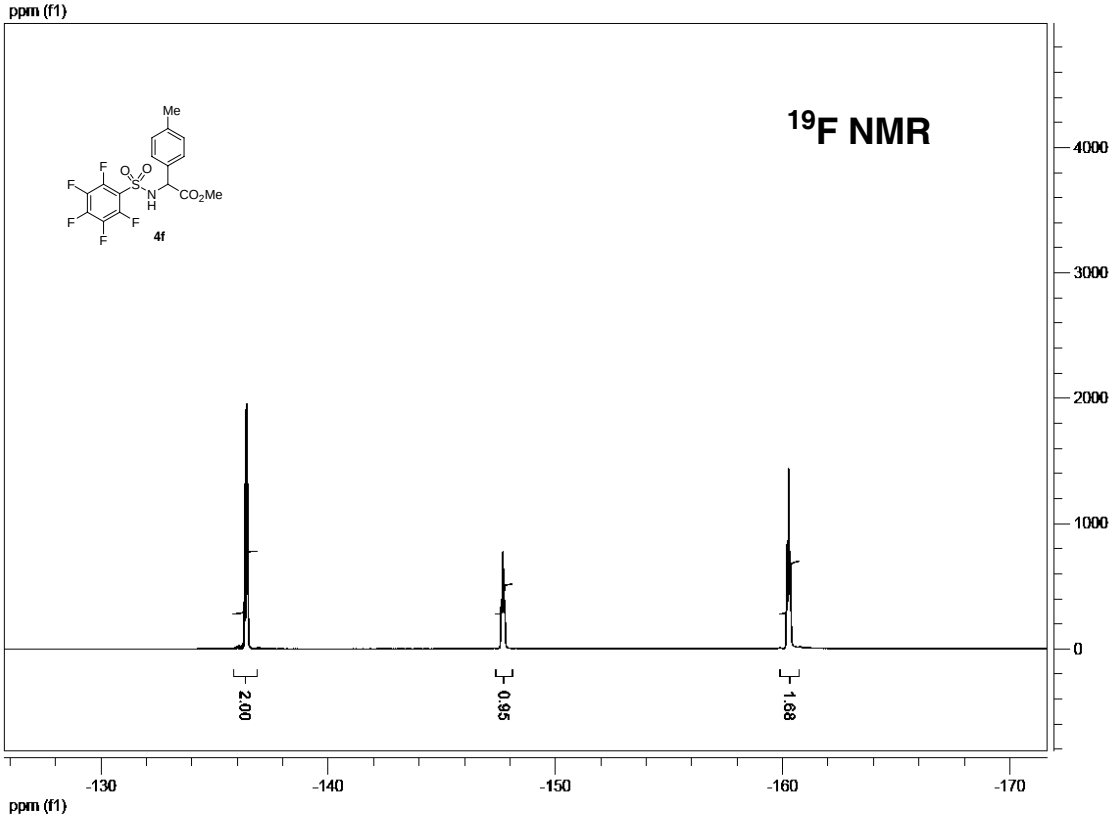

Br
F
F
F
F
F
O
O
S
N
H
CO2Me
4e
1H NMR
350
300
250
200
150
100
50
0
-50
1.78
2.00
0.87
0.88
3.19
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

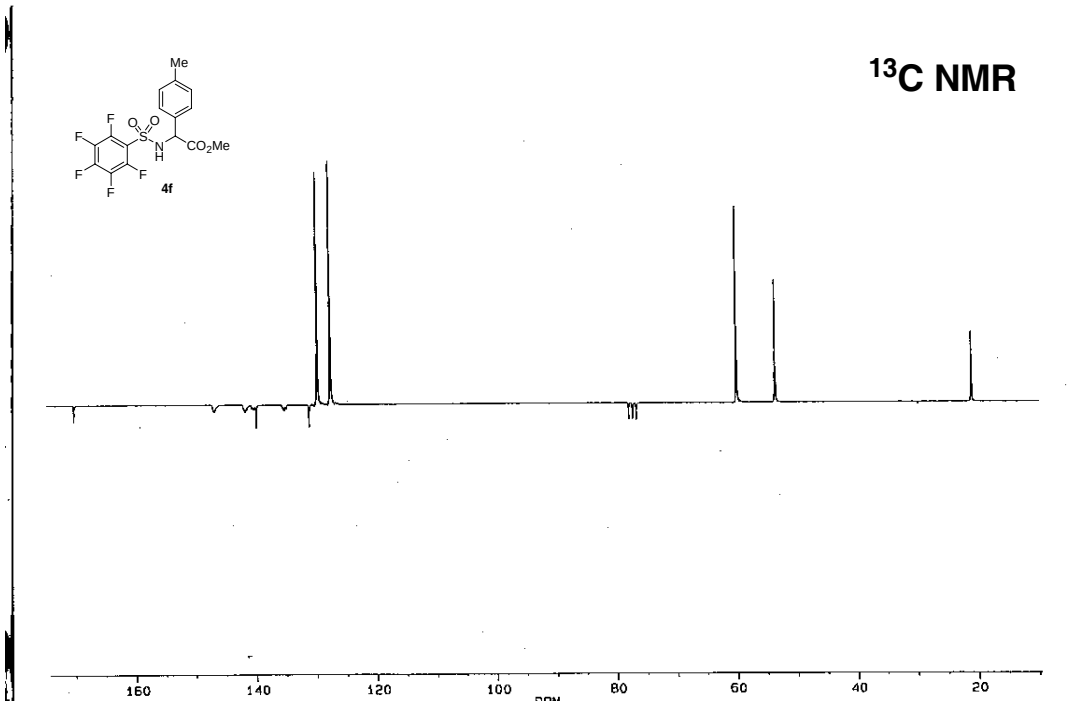

Br
F
F
F
F
F
O
O
S
N
H
CO2Me
4e
19F NMR
2500
2000
1500
1000
500
0
2.00
1.05
1.78
-130
-140
-150
-160
ppm (f1)

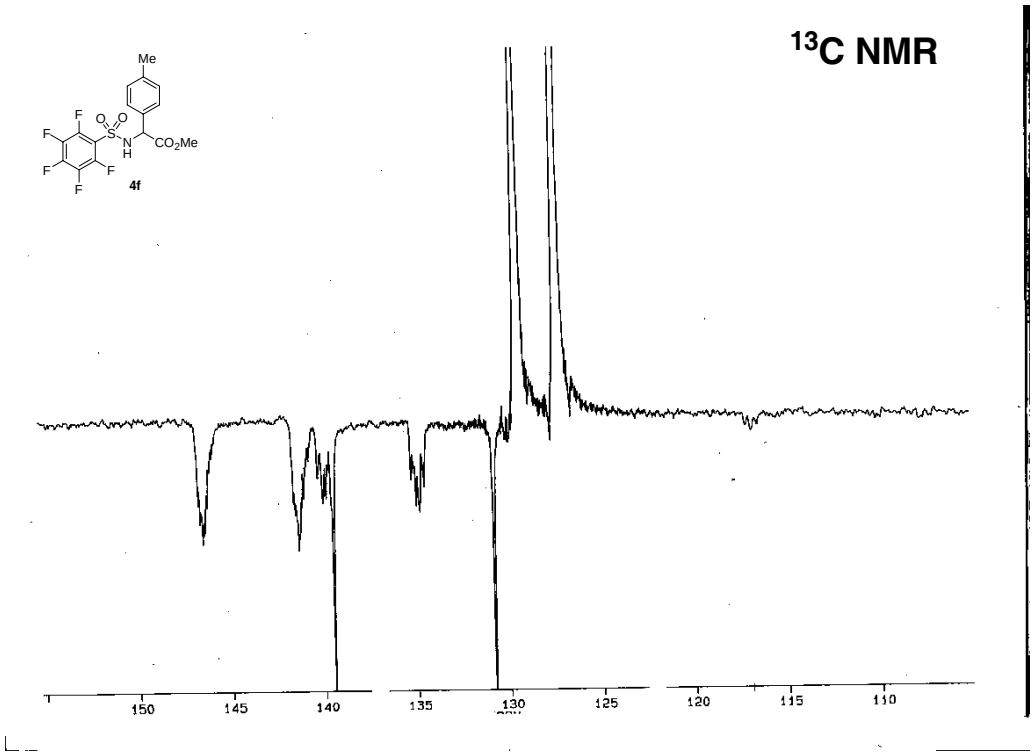

Br
F
F
F
F
F
O
O
S
N
H
CO2Me
4e
13C NMR
40000
30000
20000
10000
0
150
100
50
ppm (f1)

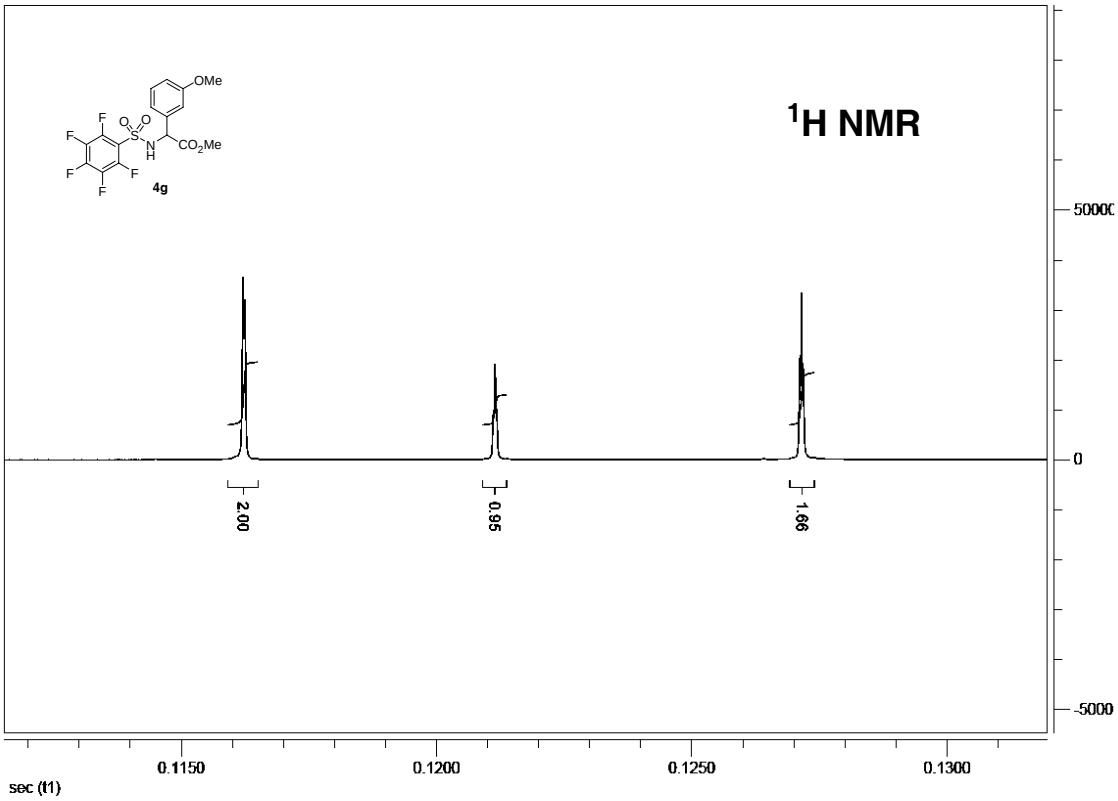

0
-5000
Br
F
F
F
F
F
O
O
S
N
H
CO2Me
4e
13C NMR
145.0
140.0
ppm (f1)

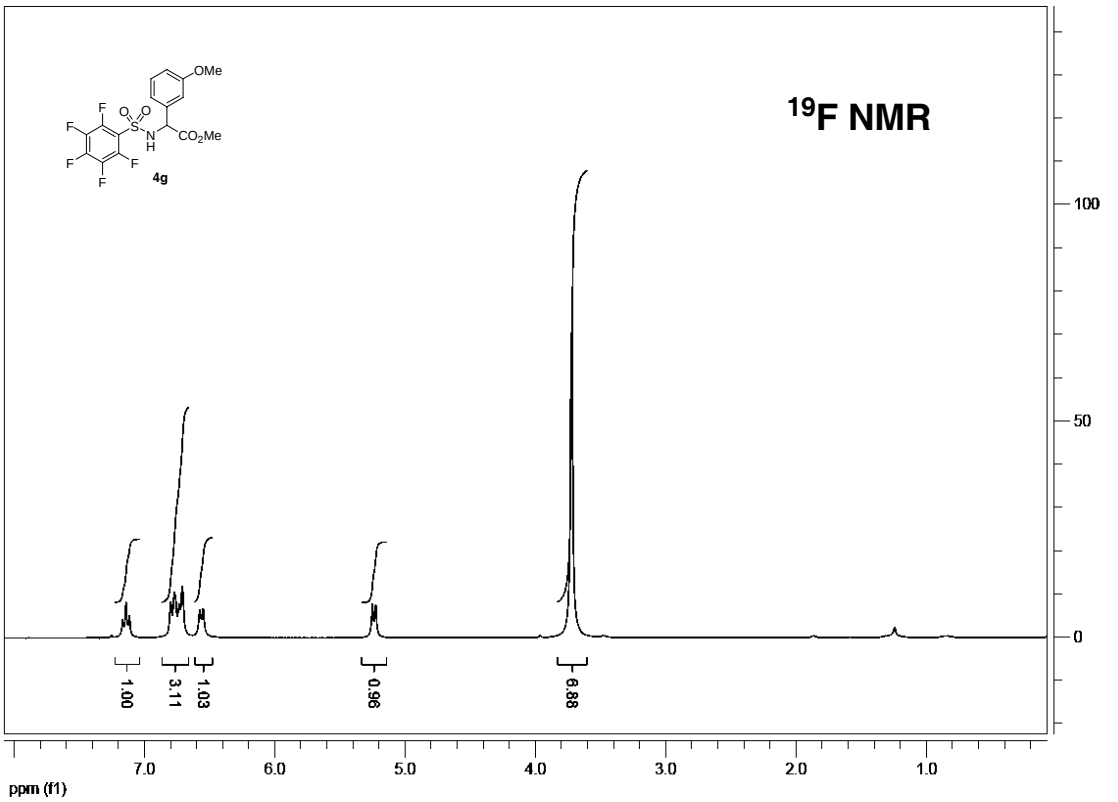

Me
F
F
F
F
F
O
O
S
N
H
CO2Me
4f
1H NMR
200
150
100
50
0
4.00
0.94
0.89
3.21
3.28
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

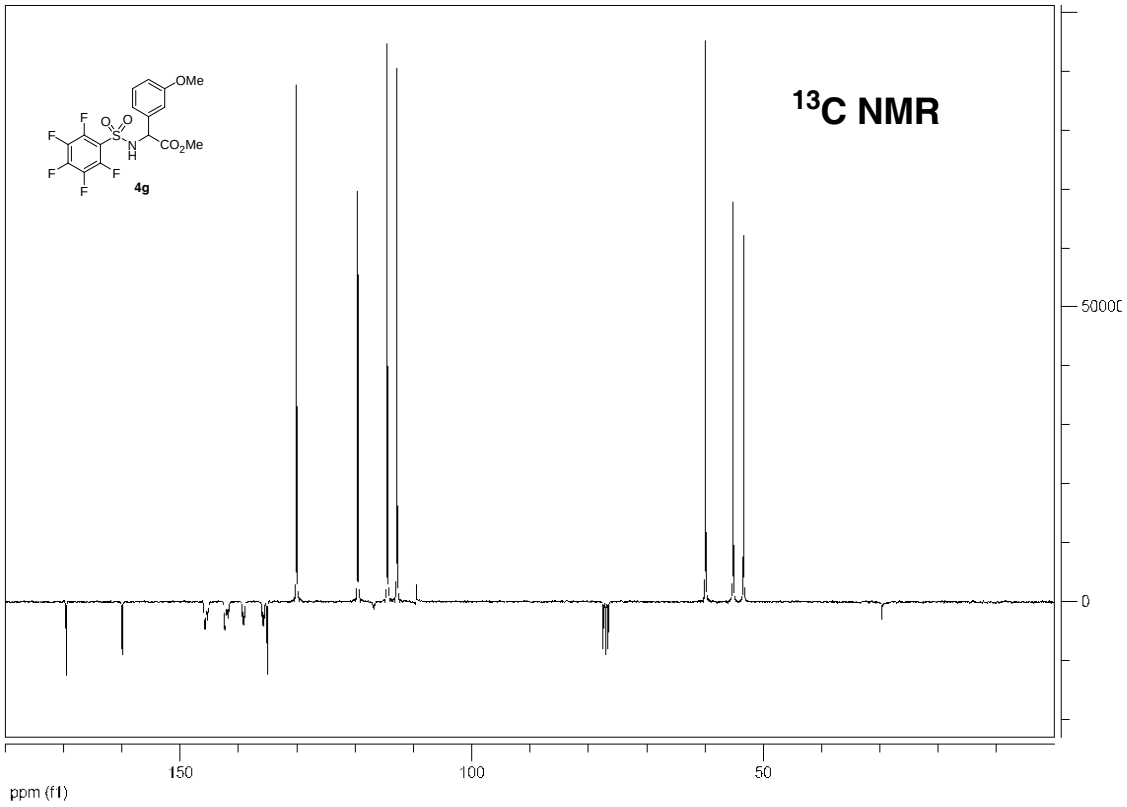

Me
F
F
F
F
F
O
O
S
N
H
CO2Me
4f
19F NMR
4000
3000
2000
1000
0
2.00
0.95
1.68
-130
-140
-150
-160
-170
ppm (f1)

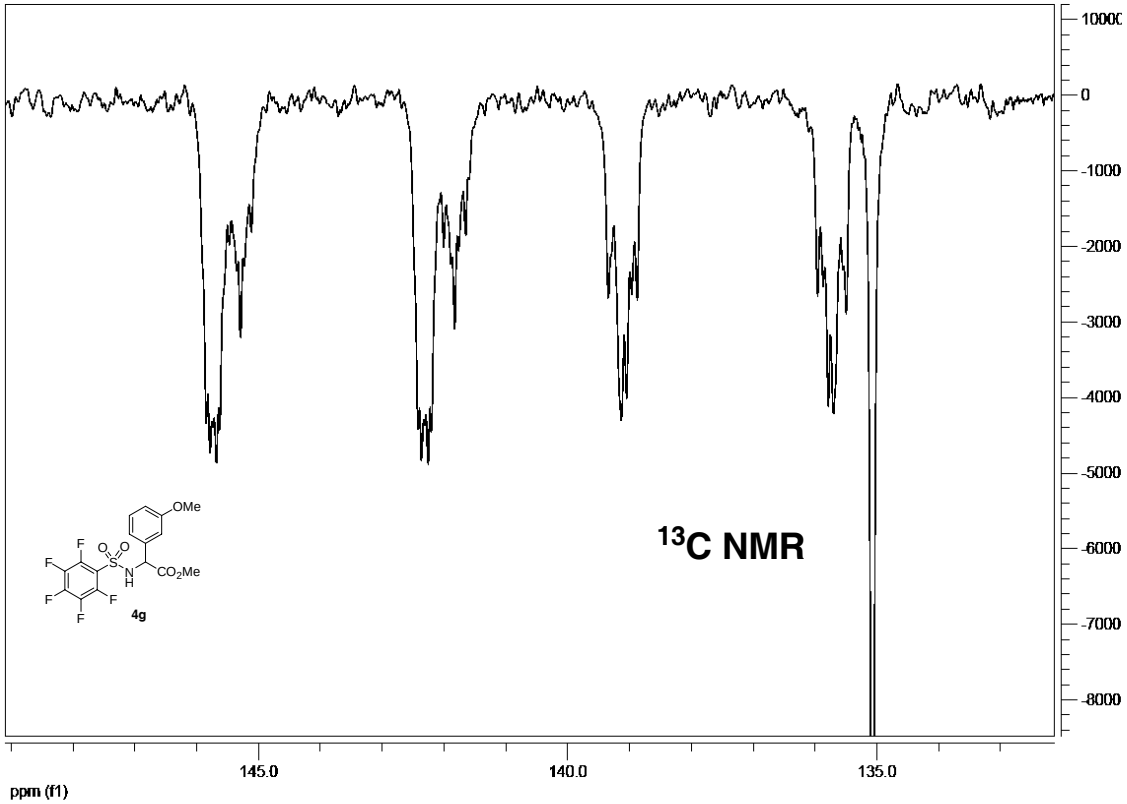

^{13}C NMR
Me
F
F
F
F
O
O
S
N
H
CO$_2$Me
4f
160
140
120
100
80
60
40
20

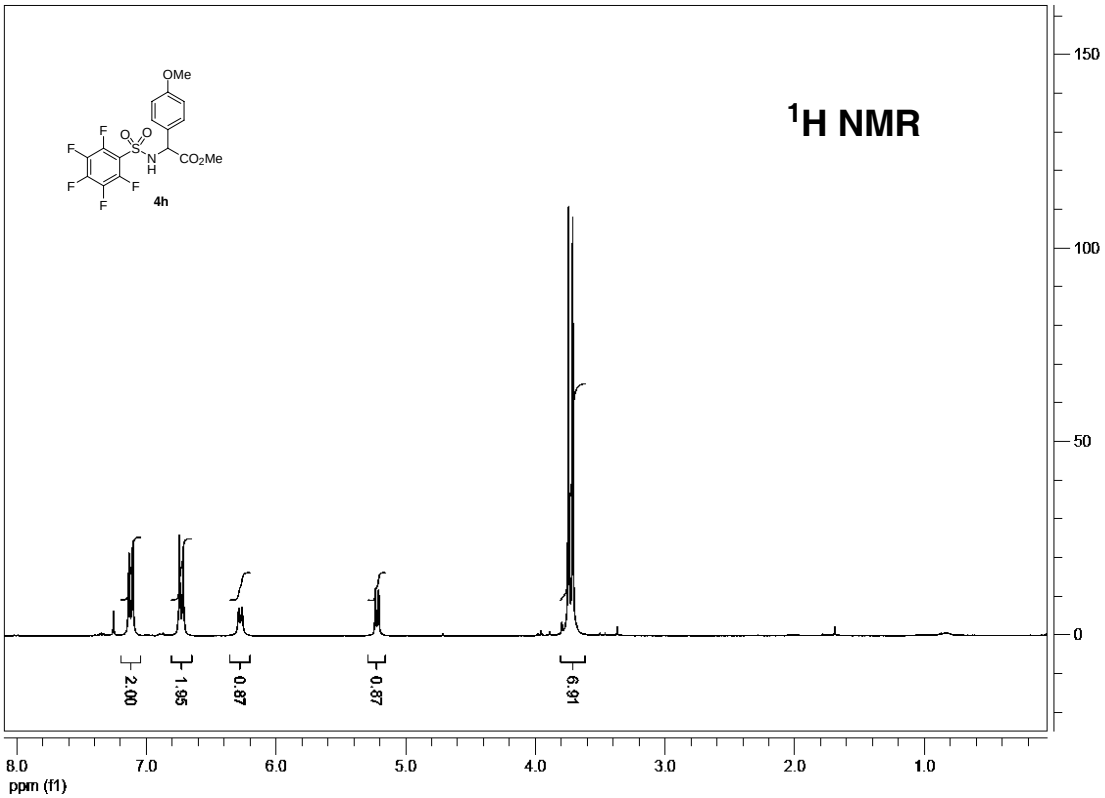

^{13}C NMR
Me
F
F
F
F
O
O
S
N
H
CO$_2$Me
4f
150
145
140
135
130
125
120
115
110

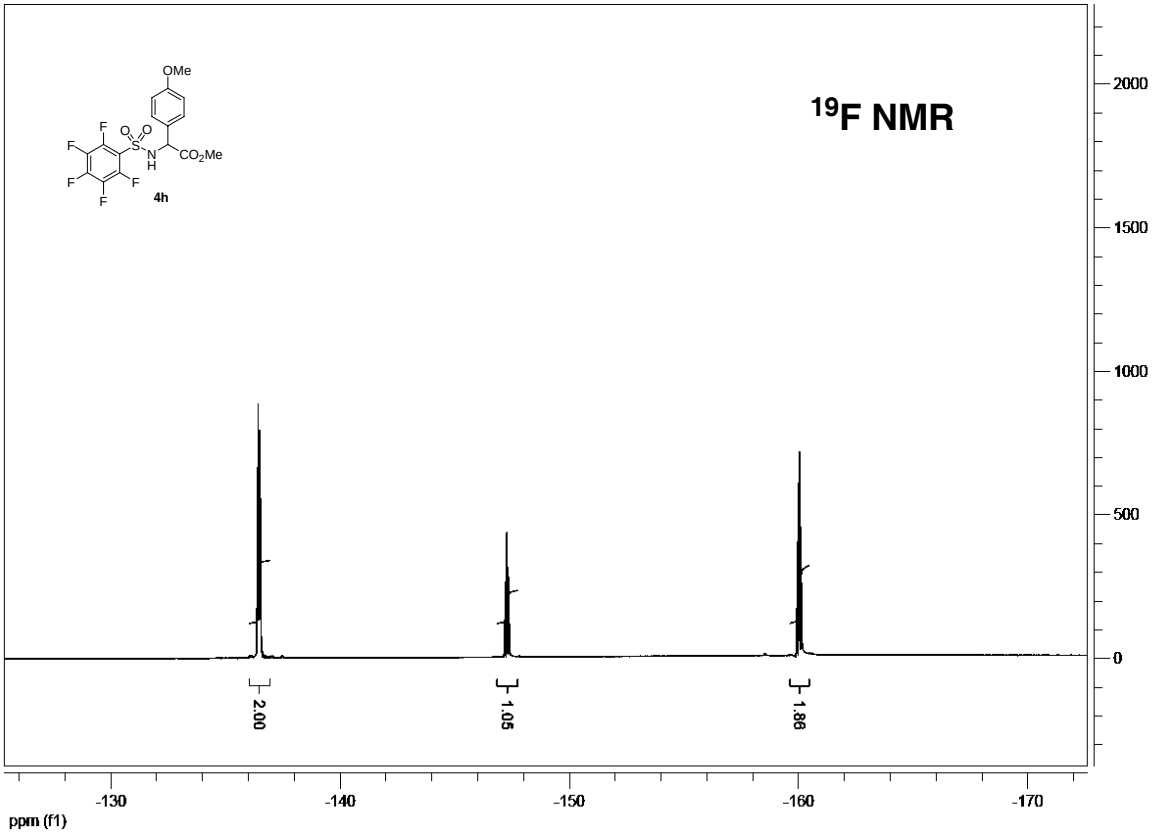

OMe
F
O
O
S
N
H
CO2Me
F
F
F
F
4g
1H NMR
50000
0
-5000
2.00
0.95
1.66
0.1150
0.1200
0.1250
0.1300
sec (f1)

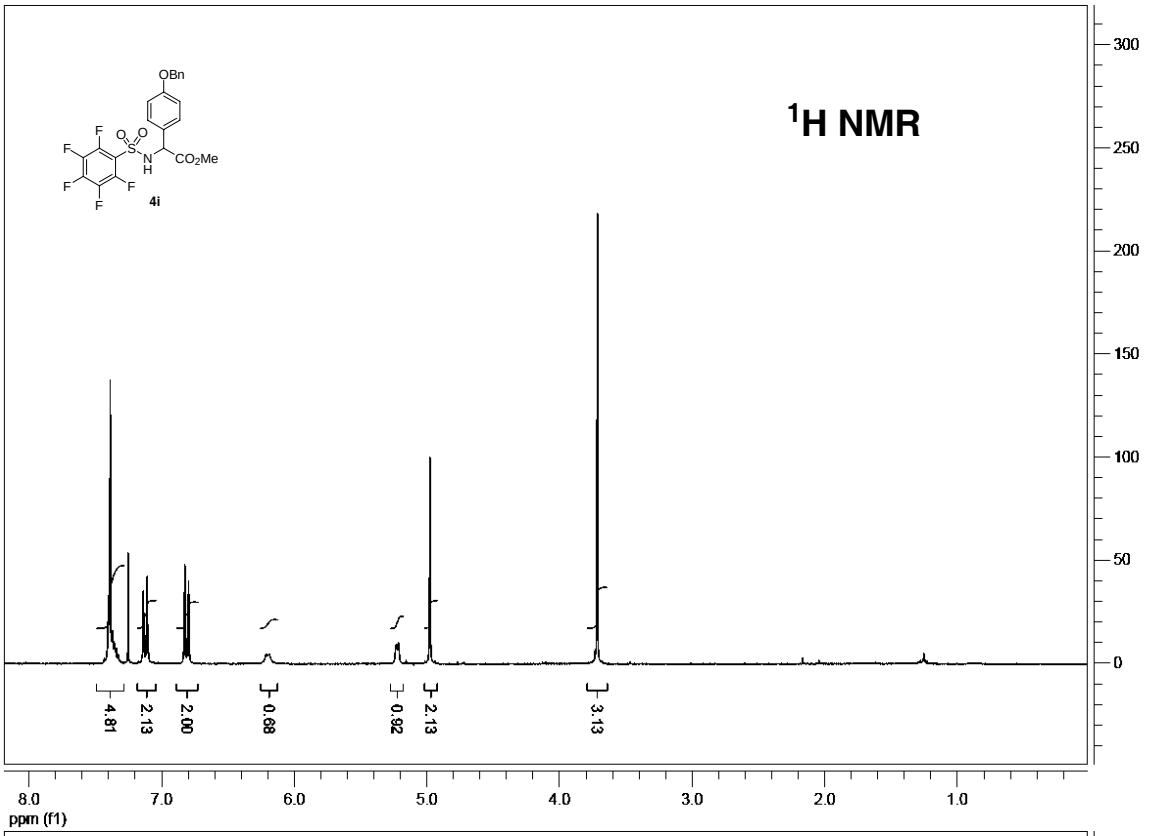

OMe
F
O
O
S
N
H
CO2Me
F
F
F
F
4g
19F NMR
100
50
0
1.00
3.11
1.03
0.96
6.88
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

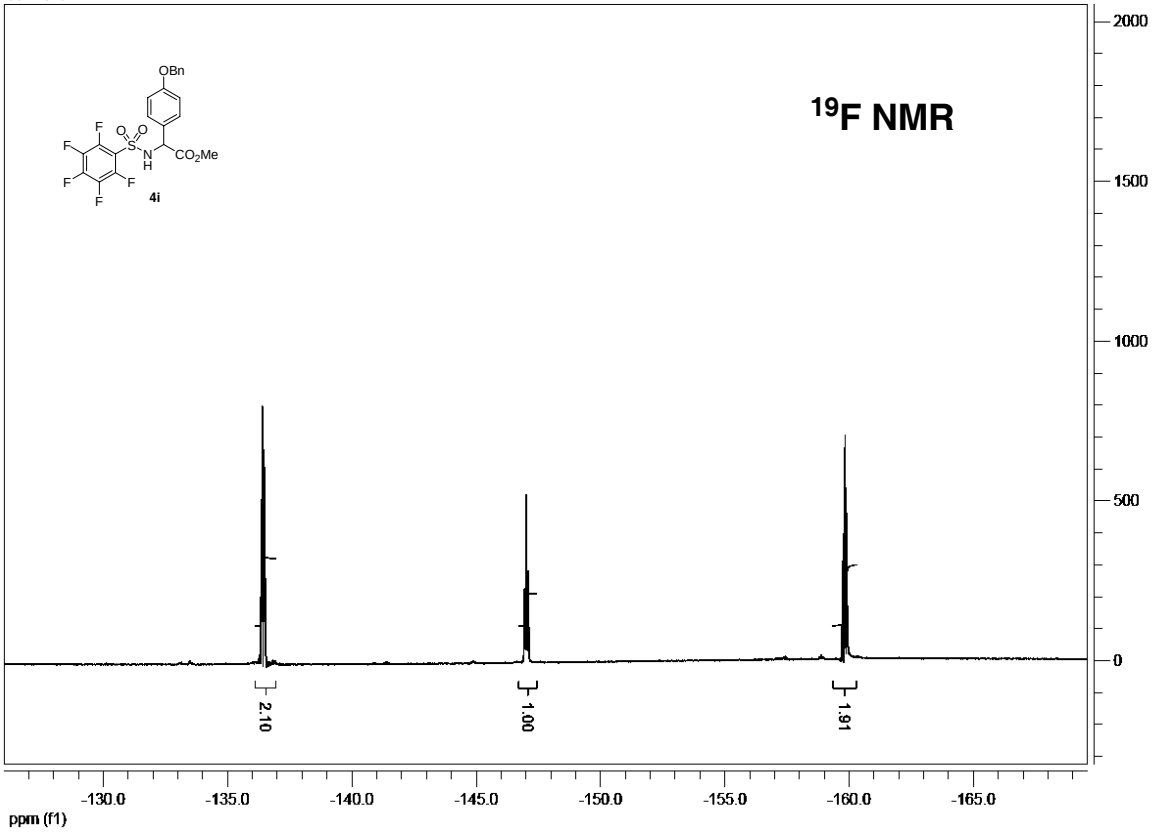

OMe
F
O
O
S
N
H
CO2Me
F
F
F
F
4g
13C NMR
50000
0
150
100
50
ppm (f1)

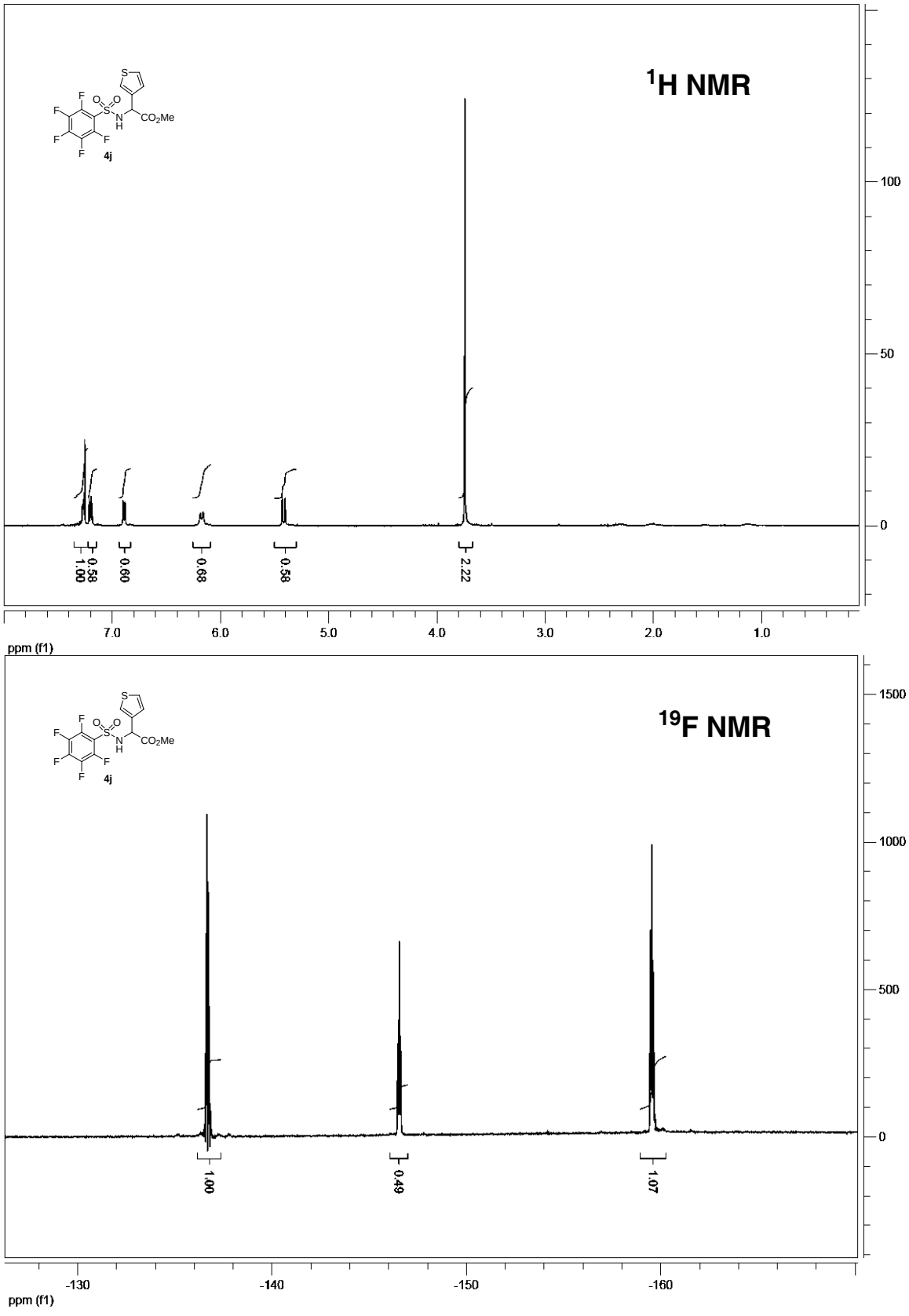

10000
0
-1000
-2000
-3000
-4000
-5000
-6000
-7000
-8000
OMe
F
O
O
S
N
H
CO2Me
F
F
F
F
4g
13C NMR
145.0
140.0
135.0
ppm (f1)

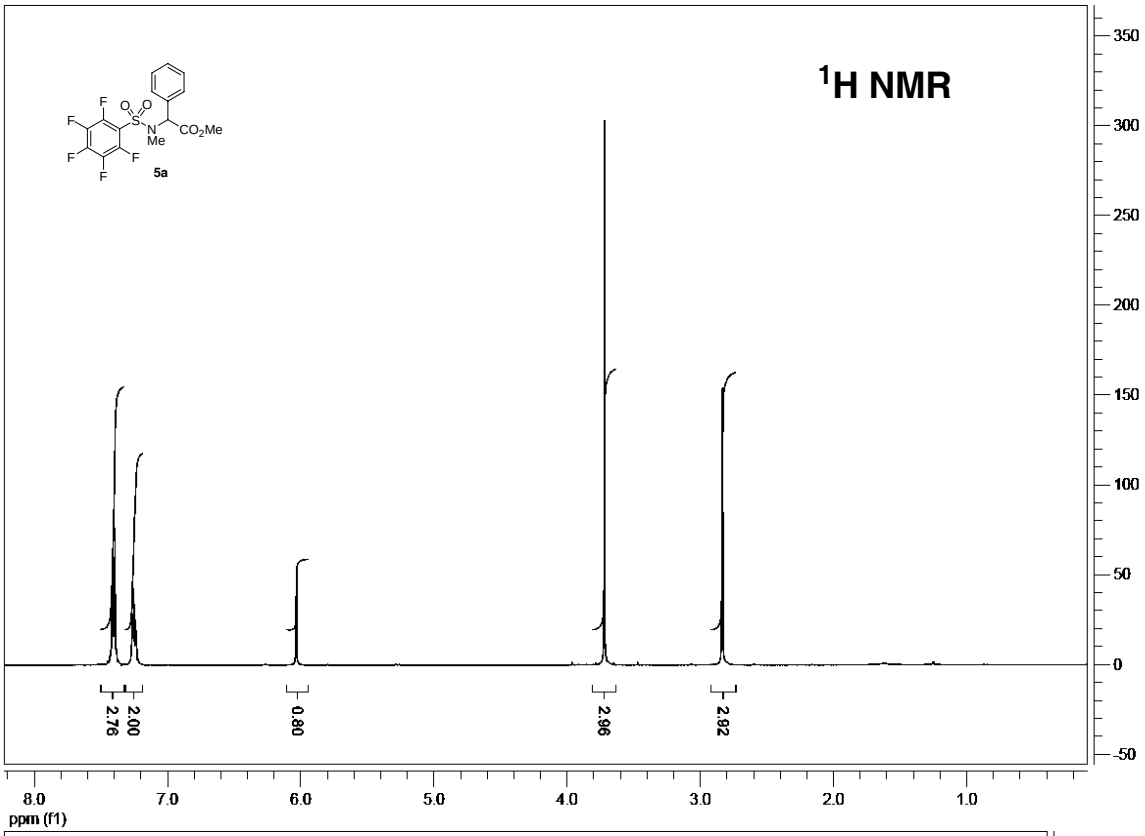

OMe
F
F
F
F
F
O
O
S
N
H
CO2Me
4h
1H NMR
150
100
50
0
2.00
1.95
0.87
0.87
6.91
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

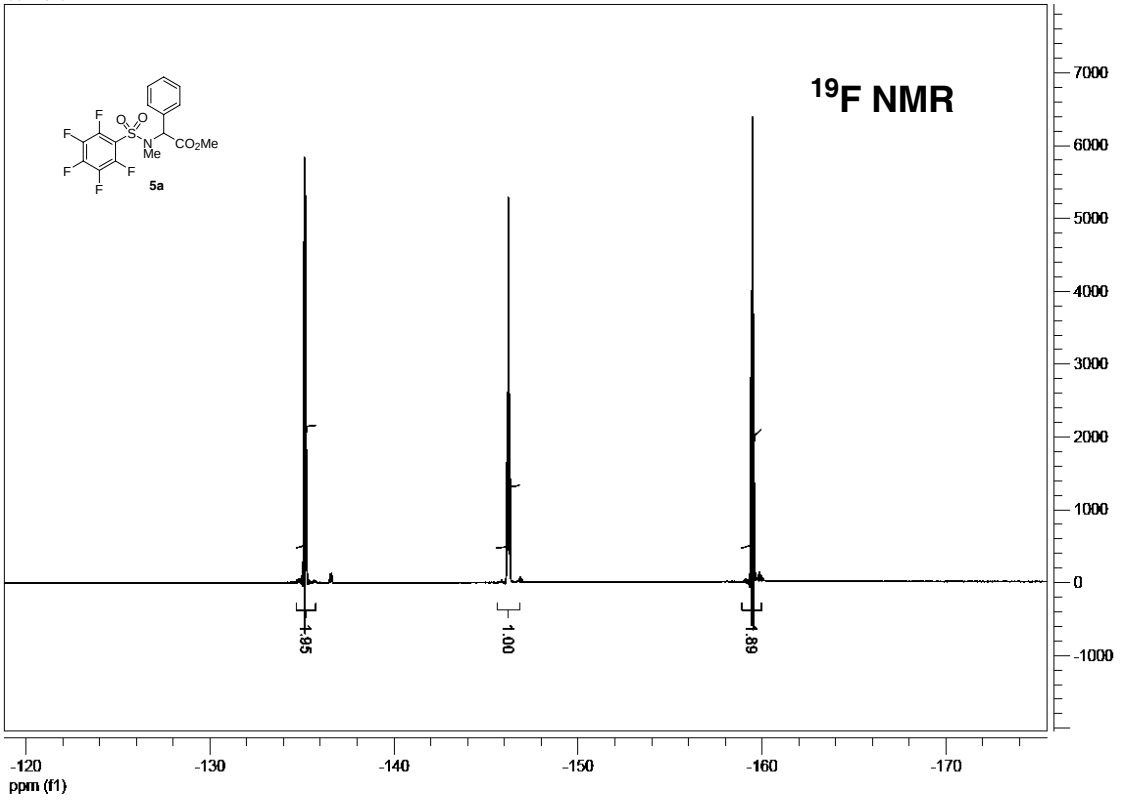

OMe
F
F
F
F
F
O
O
S
N
H
CO2Me
4h
19F NMR
2000
1500
1000
500
0
2.00
1.05
1.86
-130
-140
-150
-160
-170
ppm (f1)

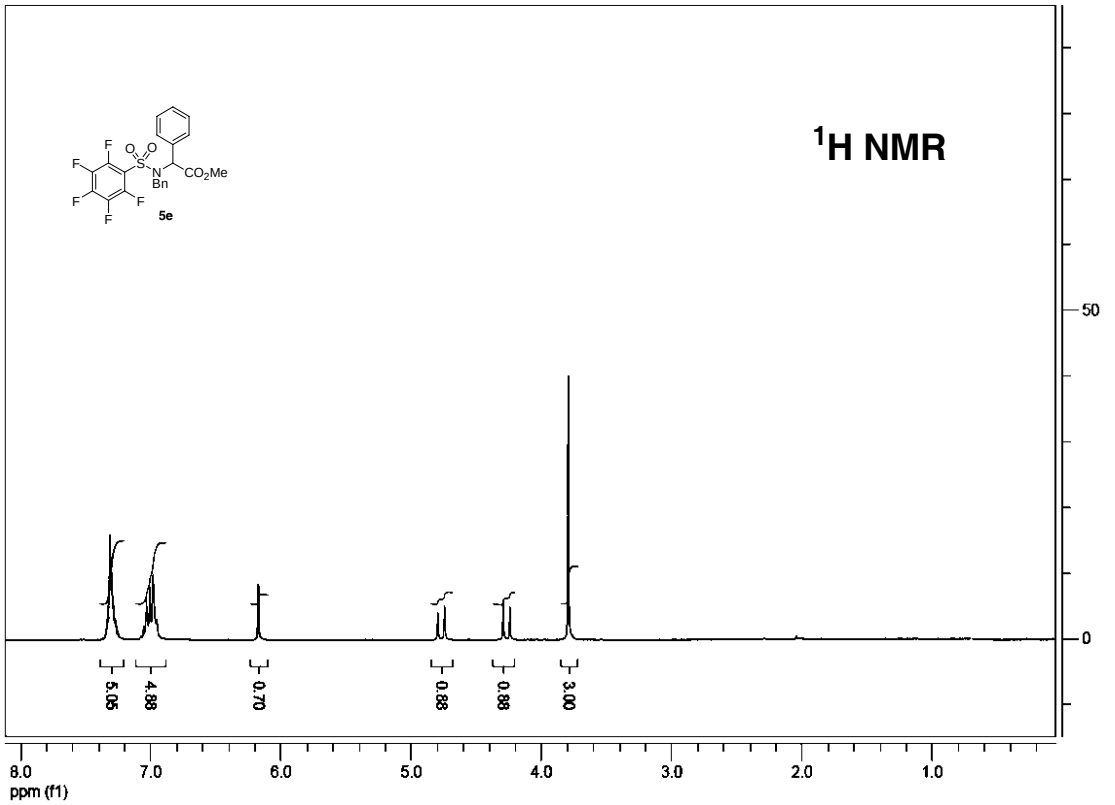

OBn
F
F
F
F
F
O
O
S
N
H
CO2Me
4i
1H NMR
4.81
2.13
2.00
0.68
0.92
2.13
3.13
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

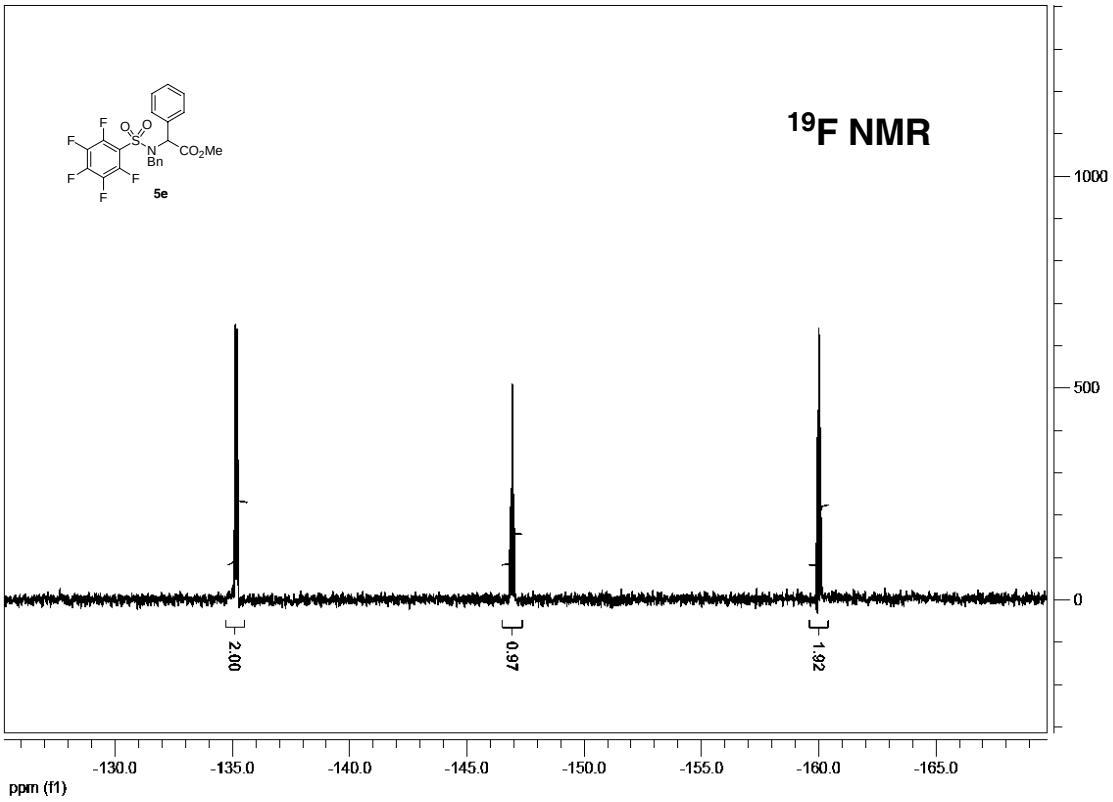

OBn
F
F
F
F
F
O
O
S
N
H
CO2Me
4i
19F NMR
2.10
1.00
1.91
-130.0
-135.0
-140.0
-145.0
-150.0
-155.0
-160.0
-165.0
ppm (f1)

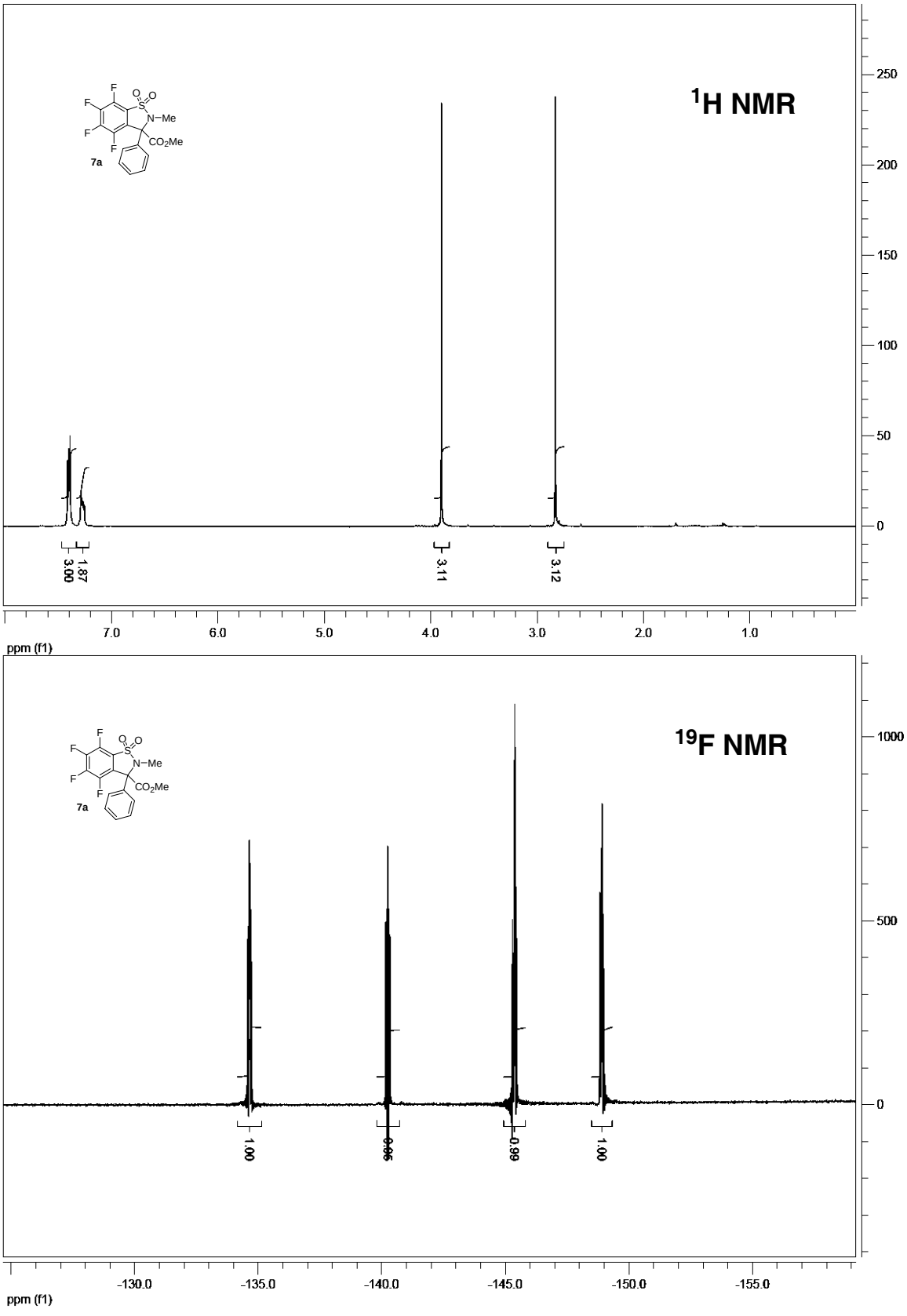

^{1}H NMR
4j
1.00
0.58
0.60
0.68
0.58
2.22
ppm (f1)
^{19}F NMR
4j
1.00
0.49
1.07
ppm (f1)

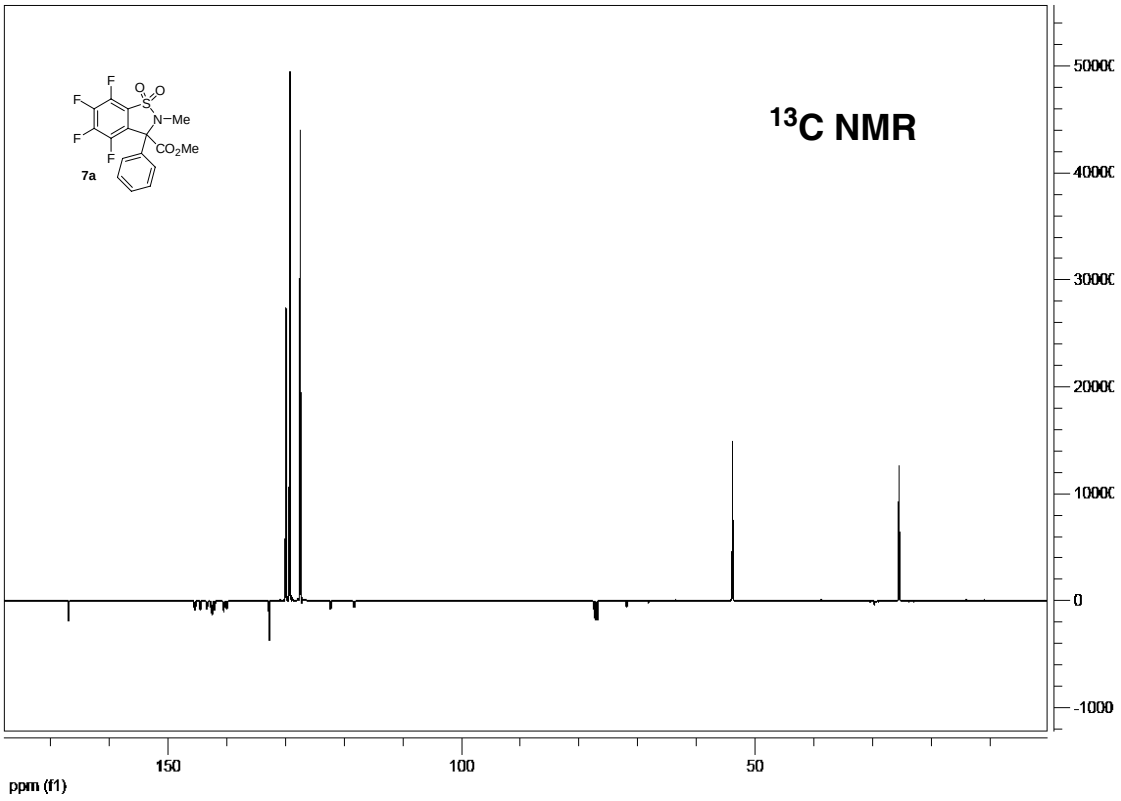

^{1}H NMR
5a
2.76
2.00
0.80
2.96
2.92
ppm (f1)

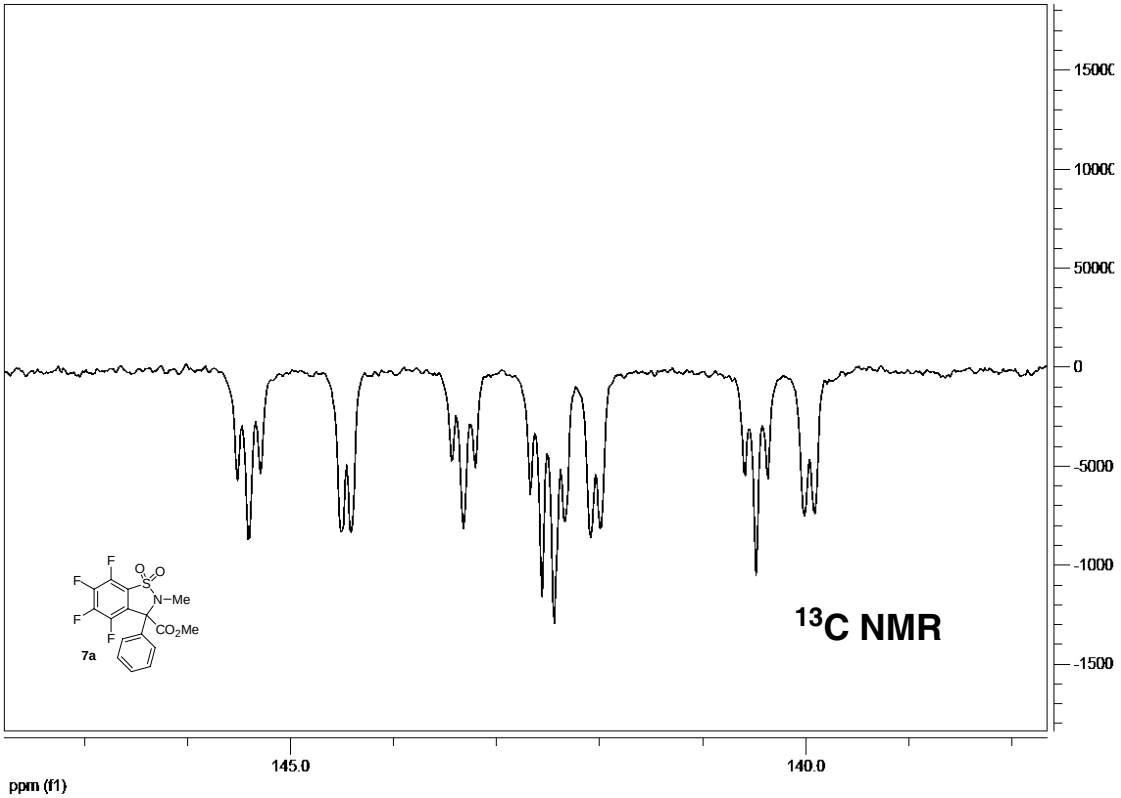

^{19}F NMR
5a
1.85
1.00
1.89
ppm (f1)

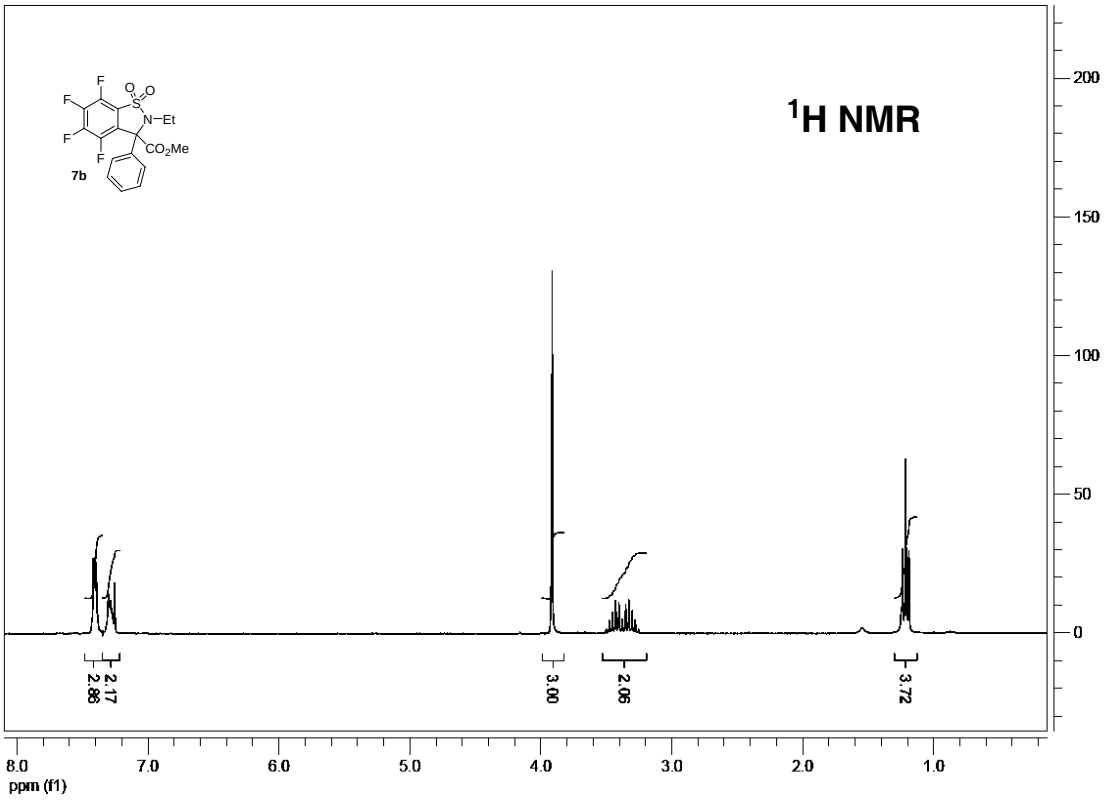

^{1}H NMR
5e
5.05
4.88
0.70
0.88
0.88
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
50
0

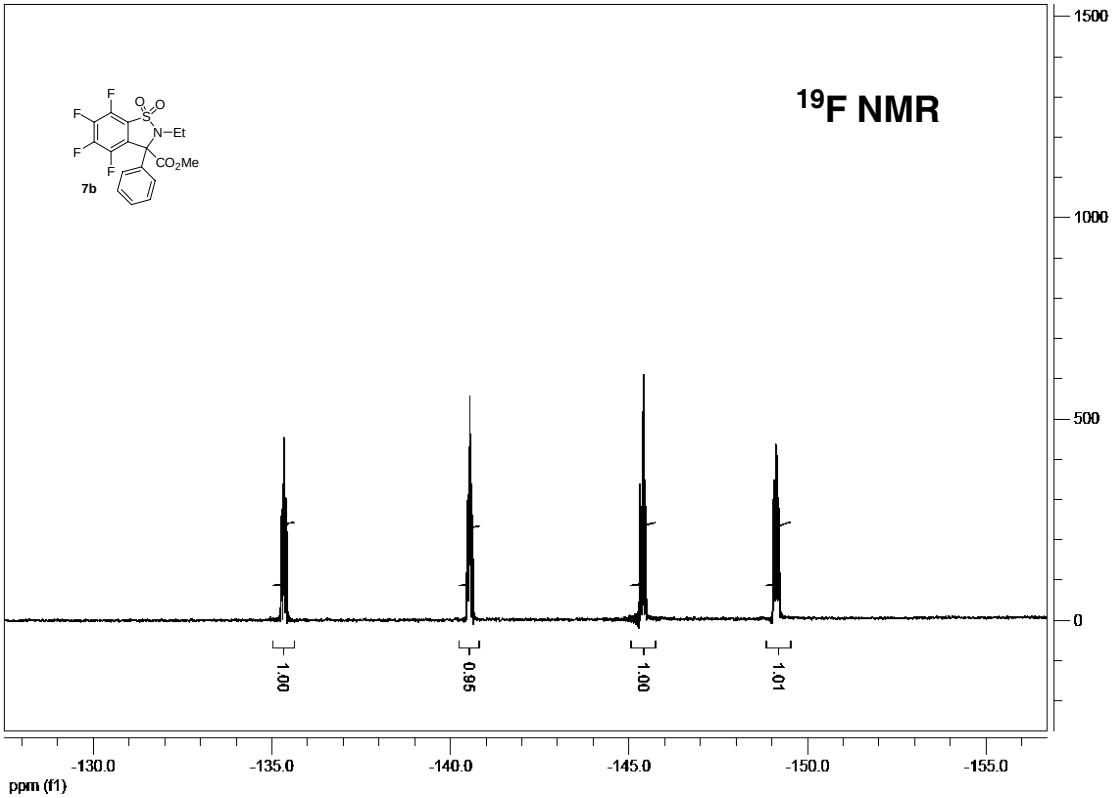

^{19}F NMR
5e
2.00
0.97
1.92
-130.0
-135.0
-140.0
-145.0
-150.0
-155.0
-160.0
-165.0
ppm (f1)
1000
500
0

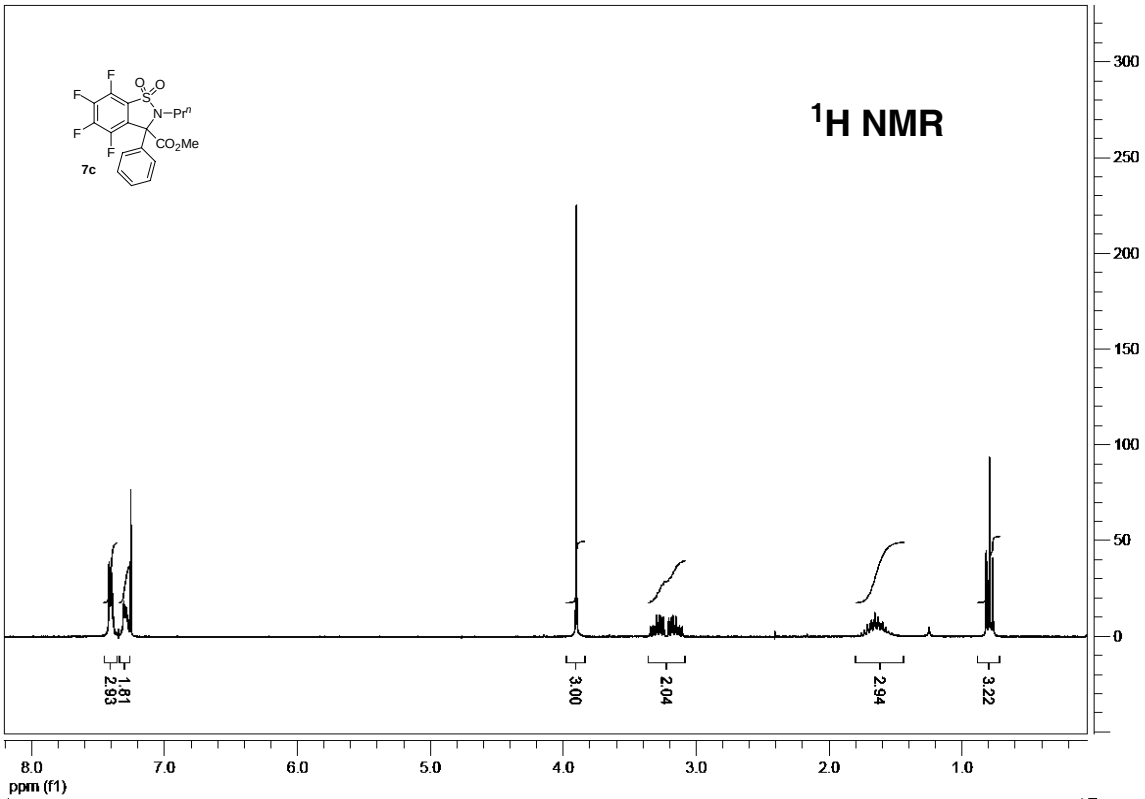

1H NMR
7a
3.00
1.87
3.11
3.12
ppm (f1)
19F NMR
7a
1.00
0.96
0.99
1.00
ppm (f1)

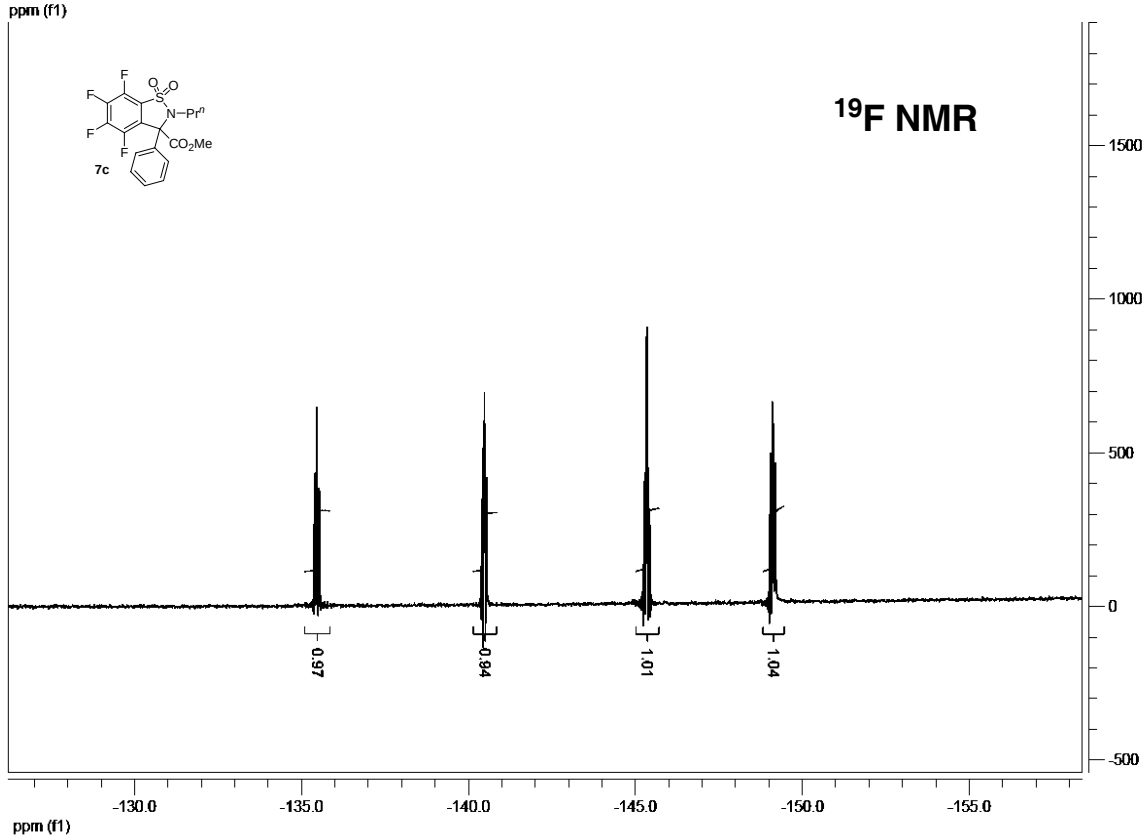

7a
13C NMR
150
100
50
ppm (f1)

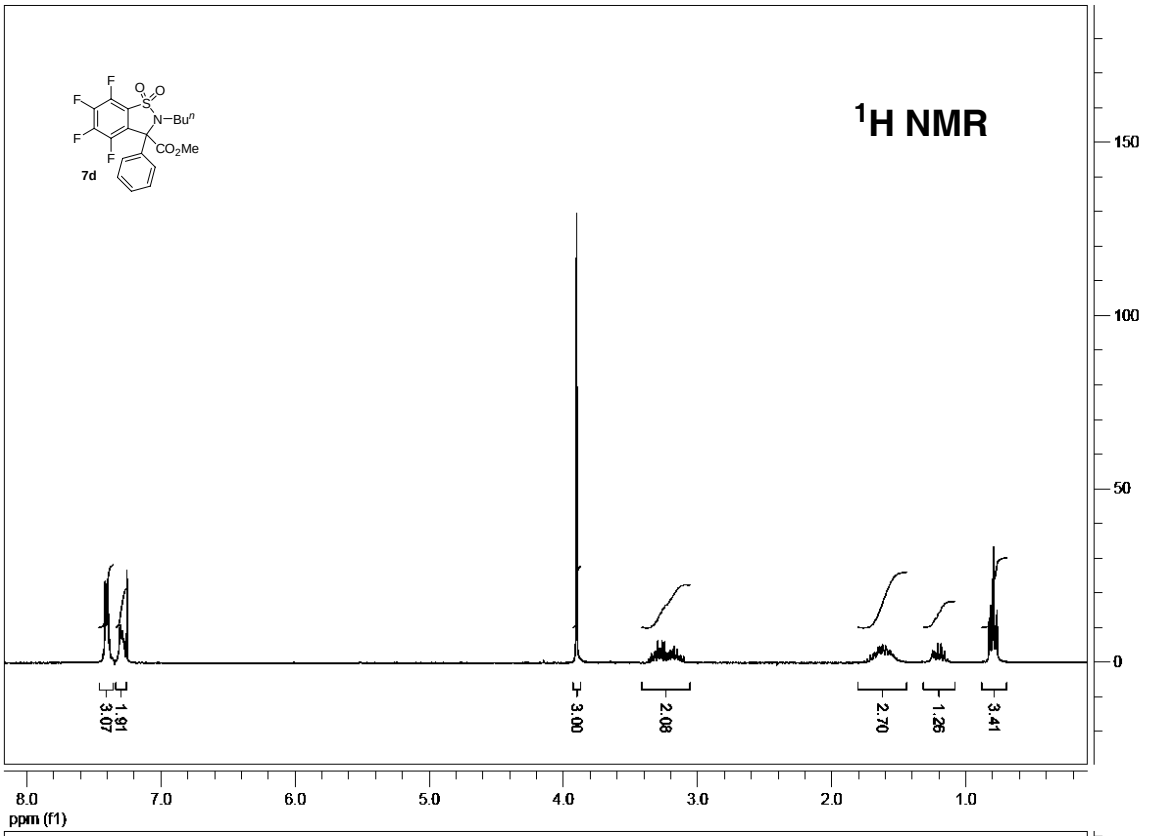

7a
13C NMR
145.0
140.0
ppm (f1)

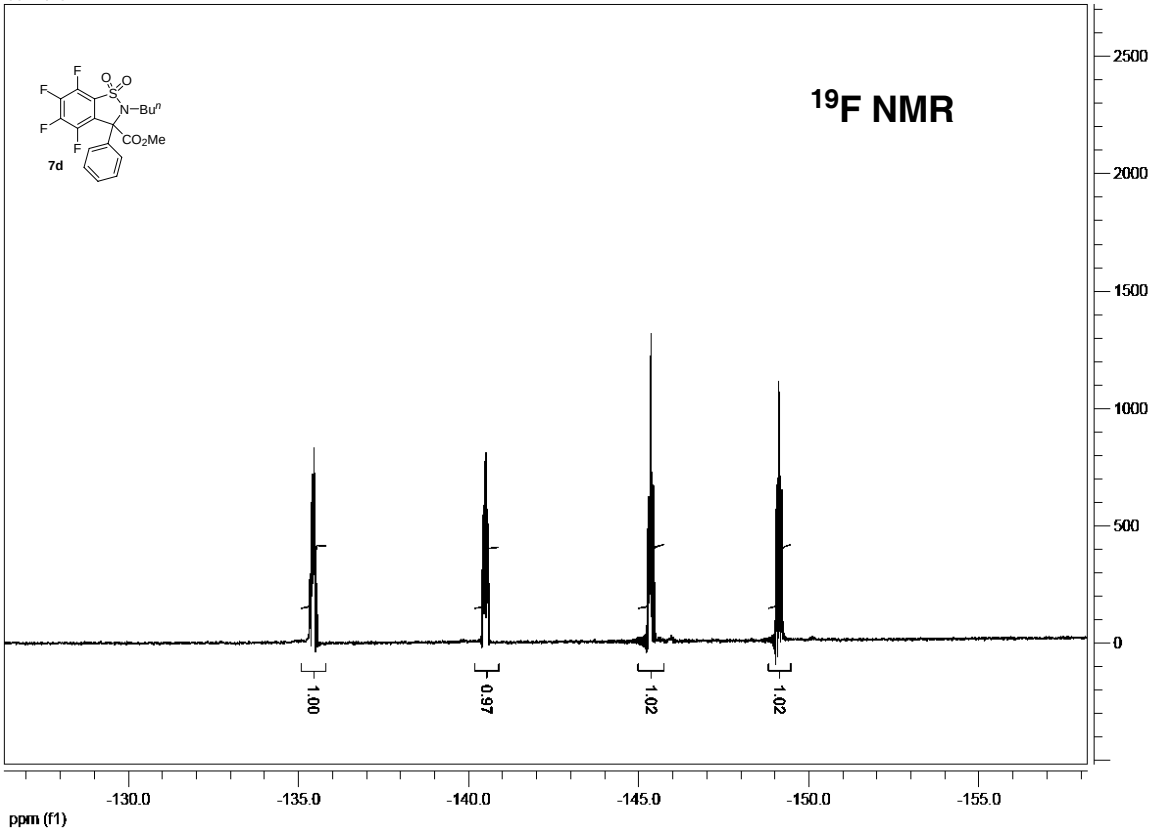

7b
^{1}H NMR
2.17
2.86
3.00
2.06
3.72
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

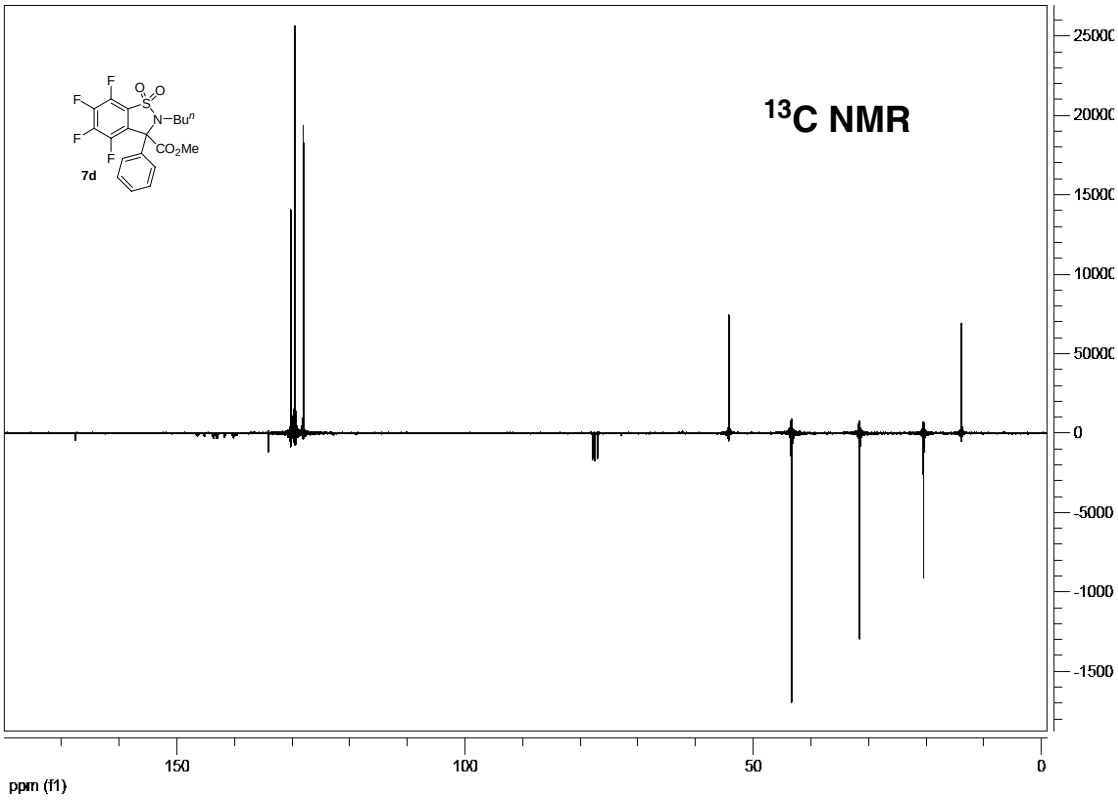

7b
^{19}F NMR
1.00
0.95
1.00
1.01
-130.0
-135.0
-140.0
-145.0
-150.0
-155.0
ppm (f1)

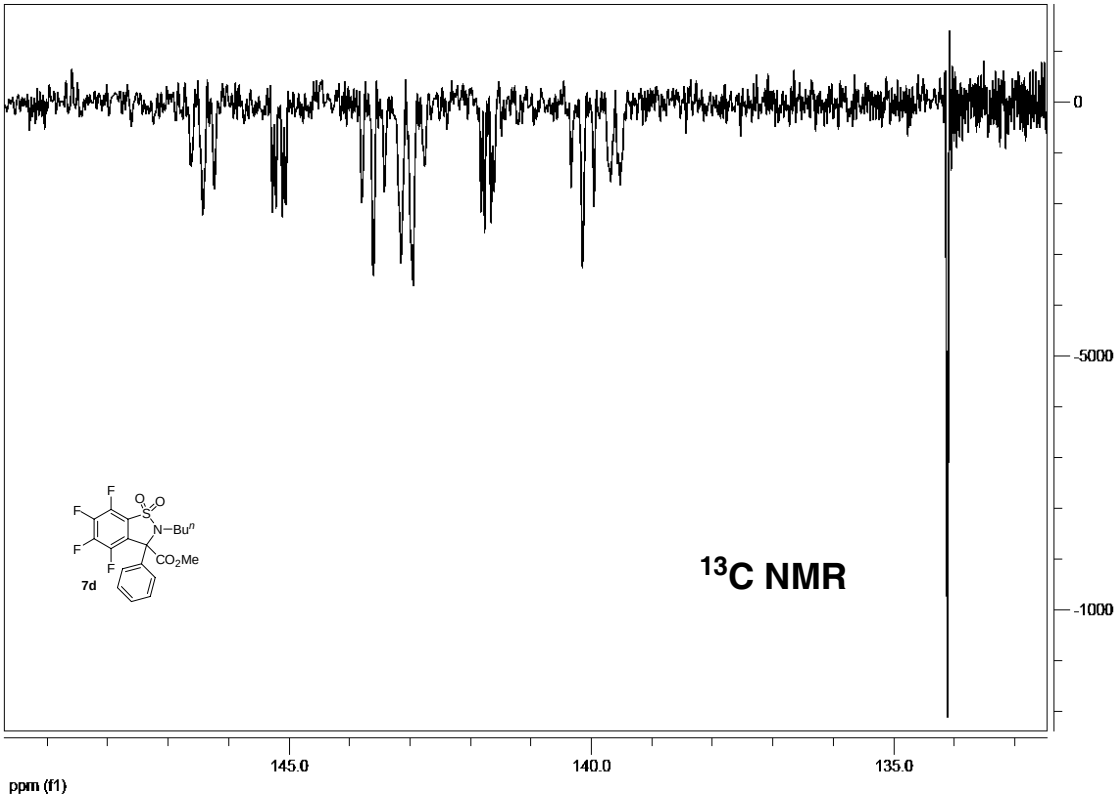

7c
^{1}H NMR
2.93
1.81
3.00
2.04
2.94
3.22
ppm (f1)

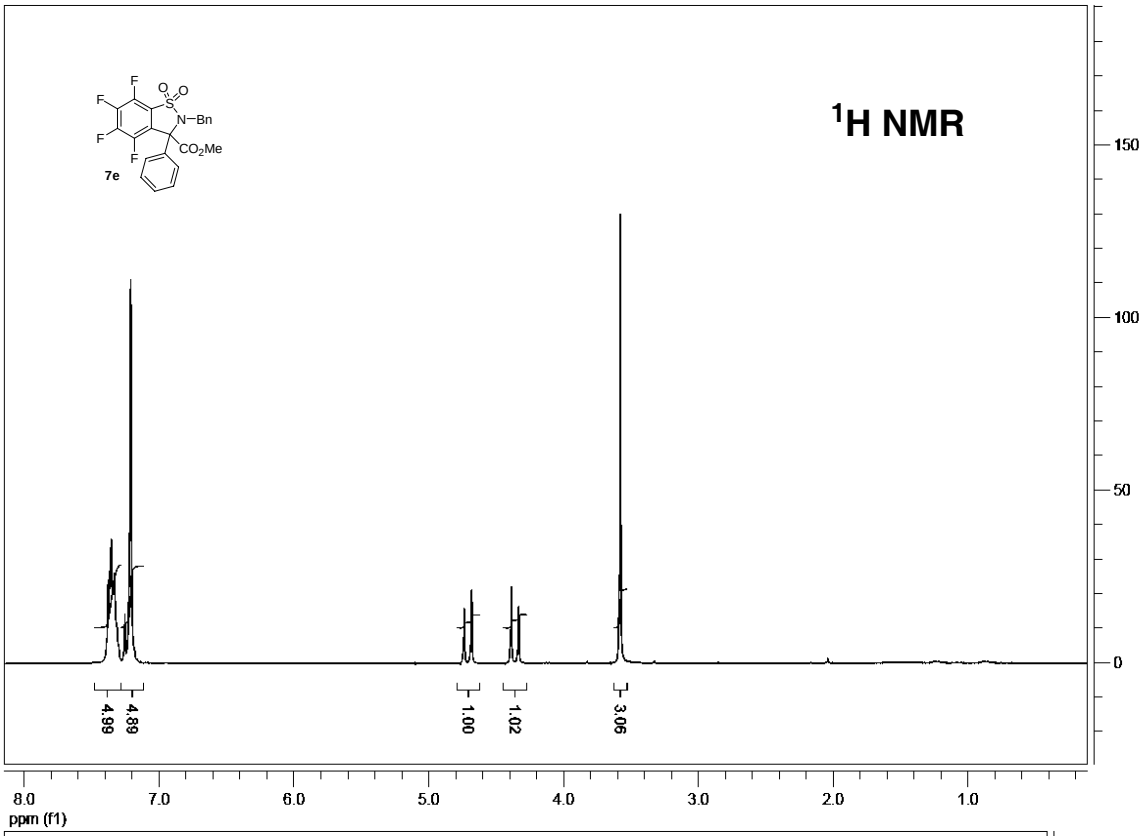

7c
^{19}F NMR
0.97
0.94
1.01
1.04
ppm (f1)

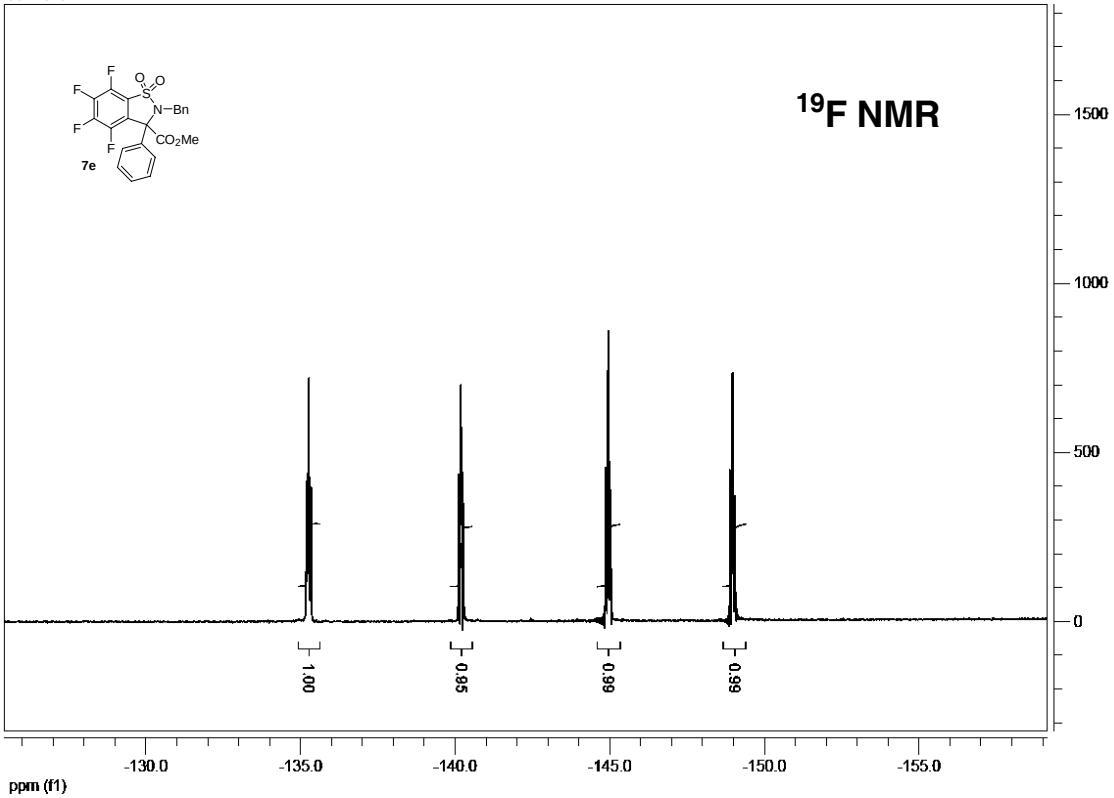

7d
^{1}H NMR
3.07
1.91
3.00
2.08
2.70
1.26
3.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

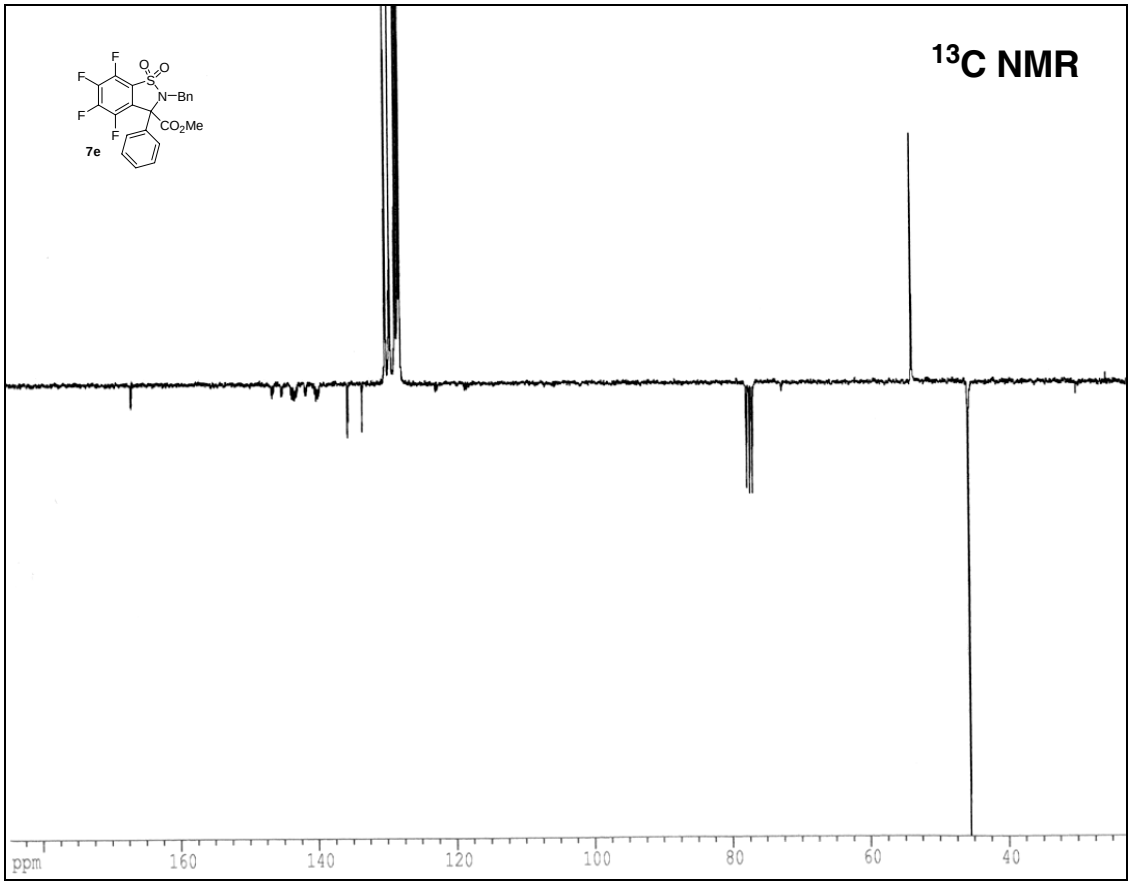

7d
^{19}F NMR
1.00
0.97
1.02
1.02
-130.0
-135.0
-140.0
-145.0
-150.0
-155.0
ppm (f1)

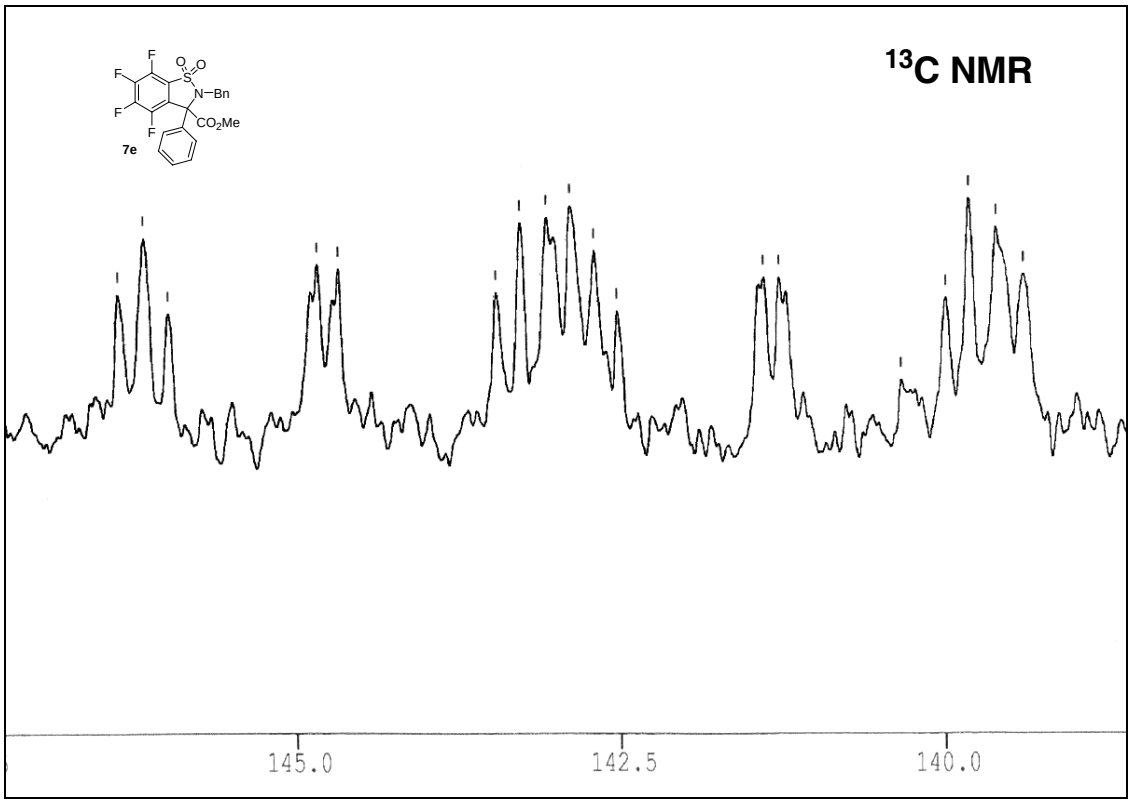

7d
^{13}C NMR
25000
20000
15000
10000
5000
0
-5000
-1000
-1500
150
100
50
0
ppm (f1)

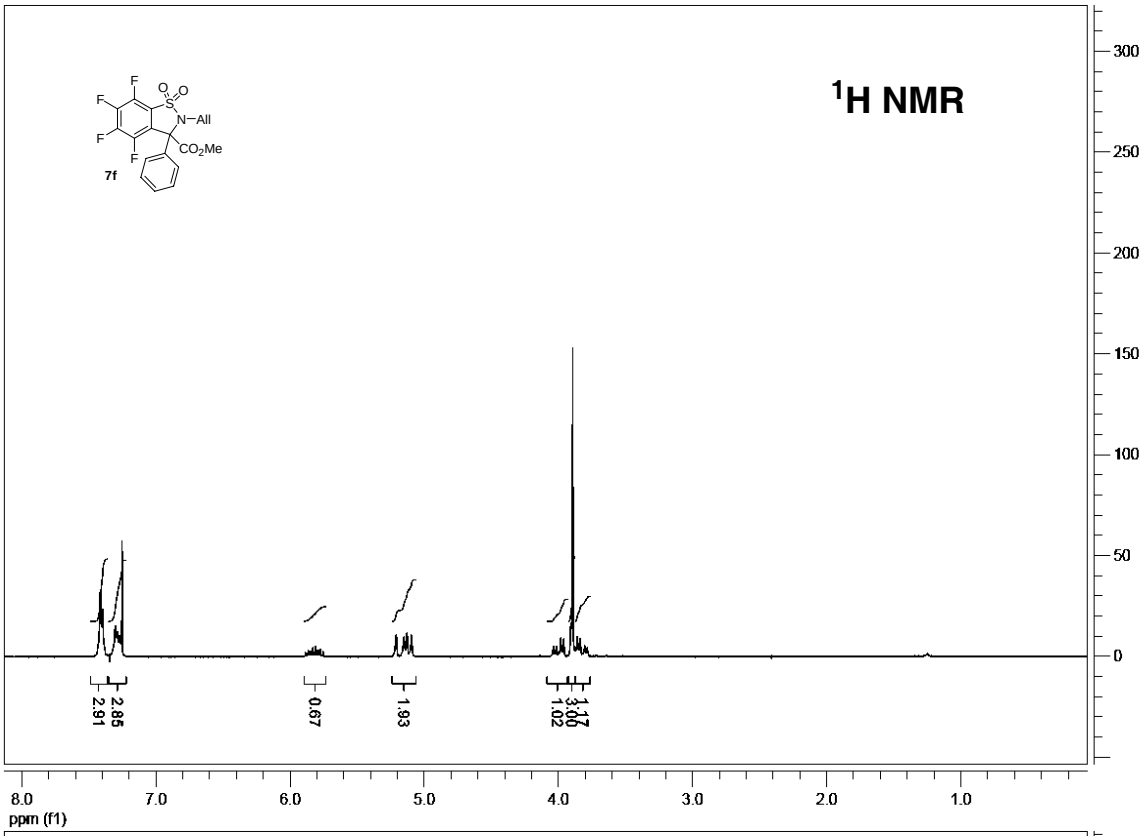

7d
^{13}C NMR
0
-5000
-1000
145.0
140.0
135.0
ppm (f1)

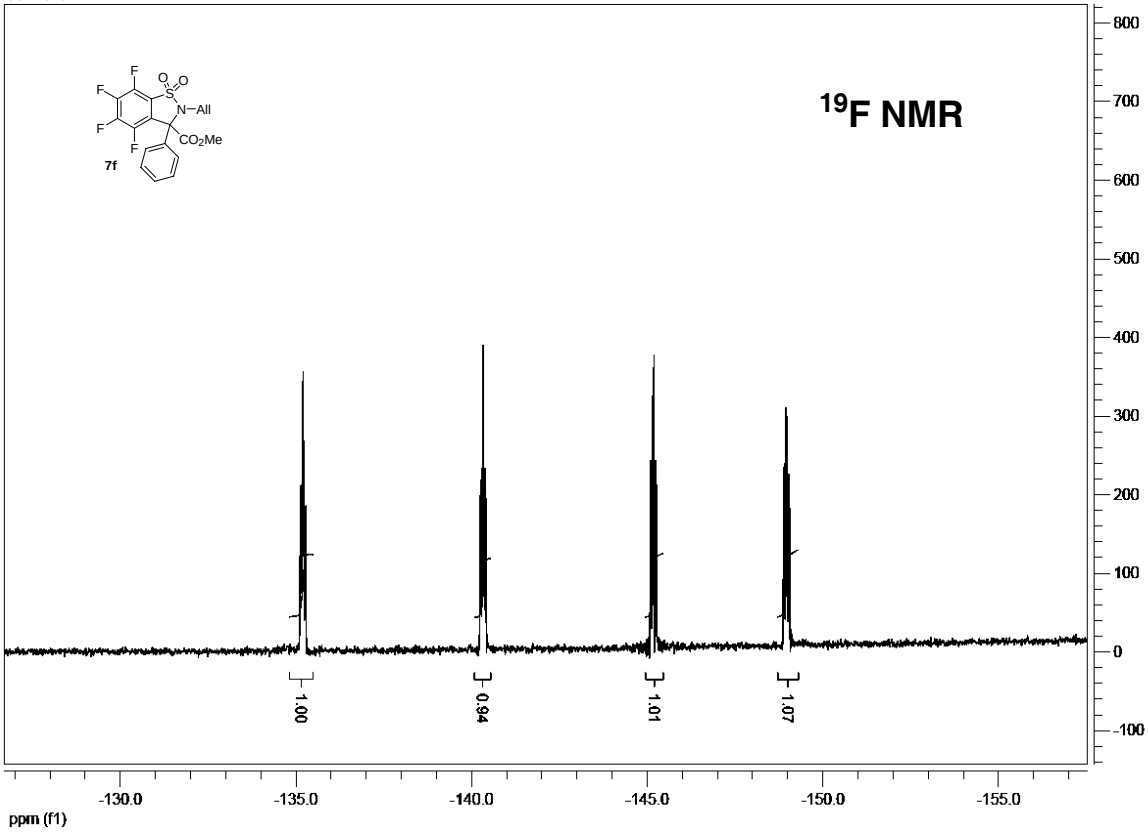

7e
^{1}H NMR
4.99
4.89
1.00
1.02
3.06
ppm (f1)

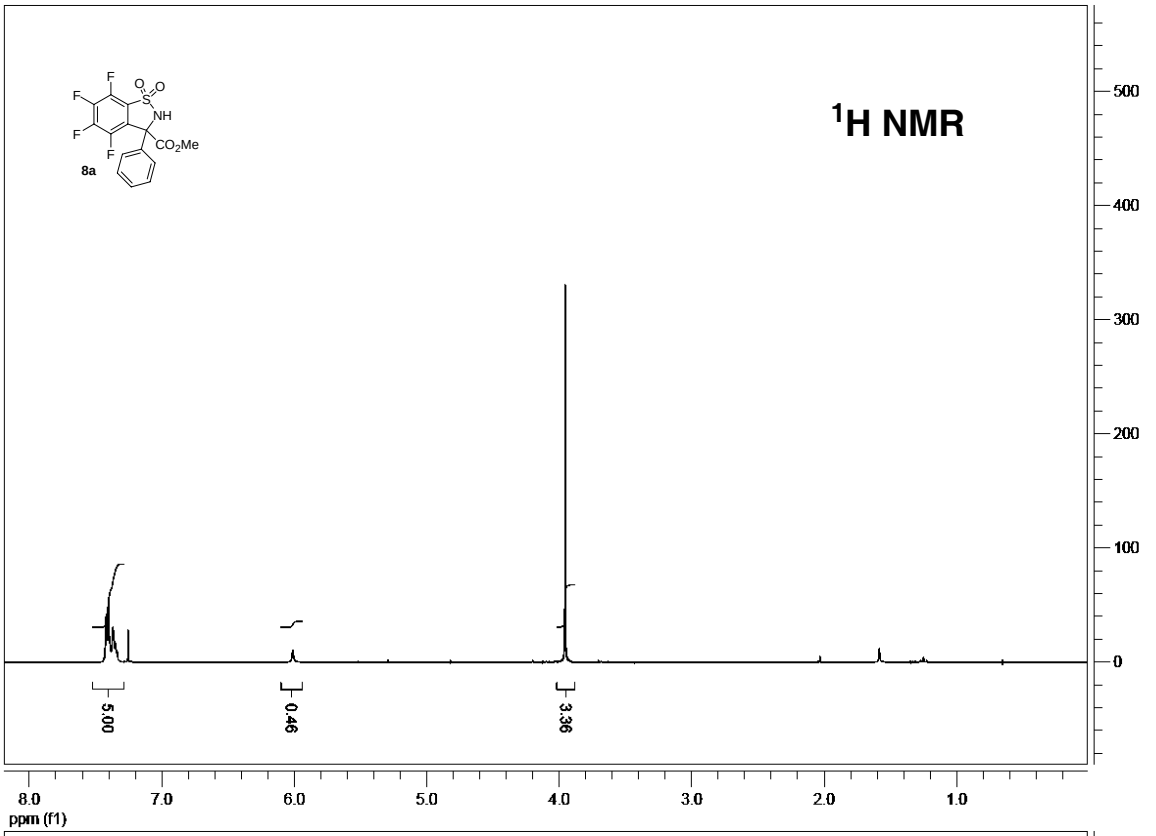

7e
^{19}F NMR
1.00
0.85
0.99
0.99
ppm (f1)

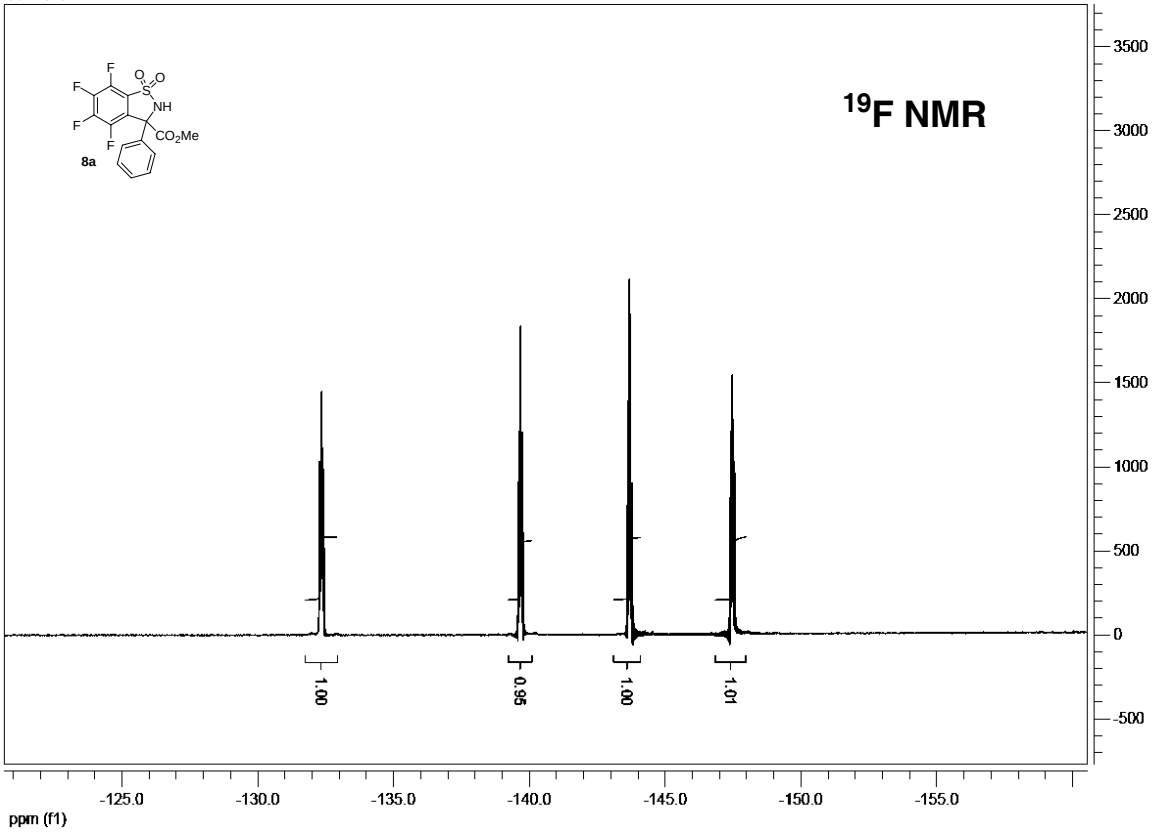

^{13}C NMR
7e
ppm
160
140
120
100
80
60
40

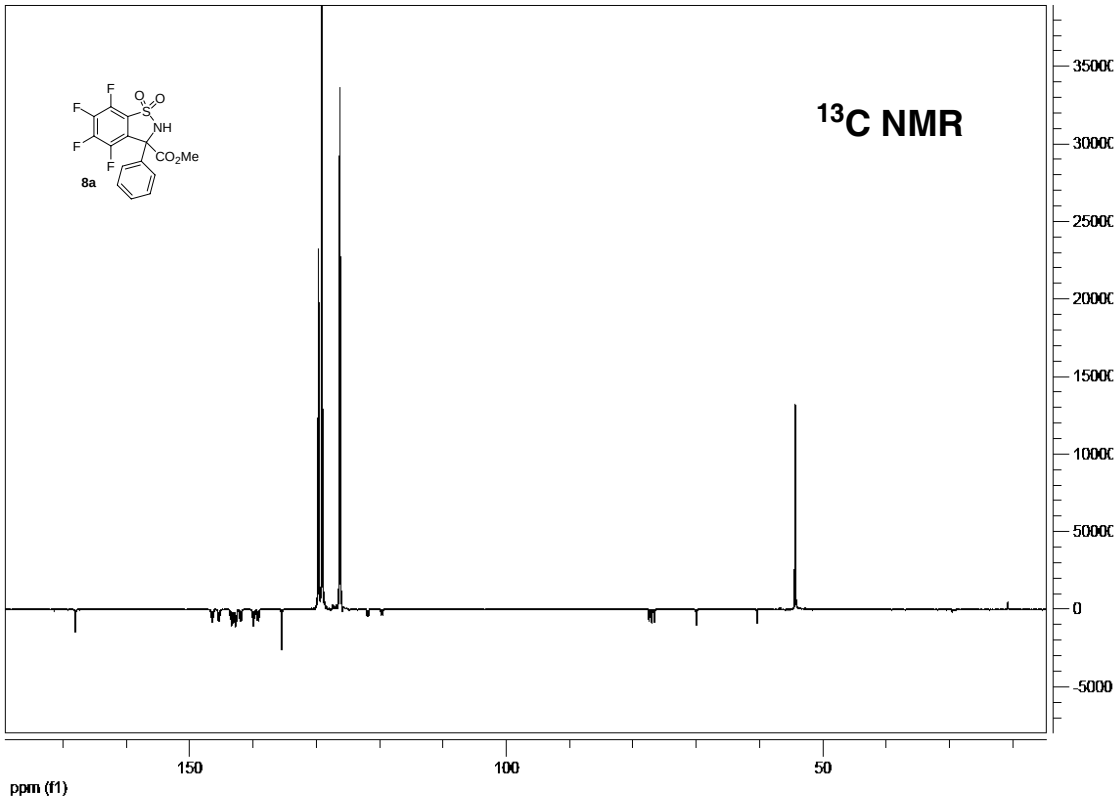

^{13}C NMR
7e
145.0
142.5
140.0

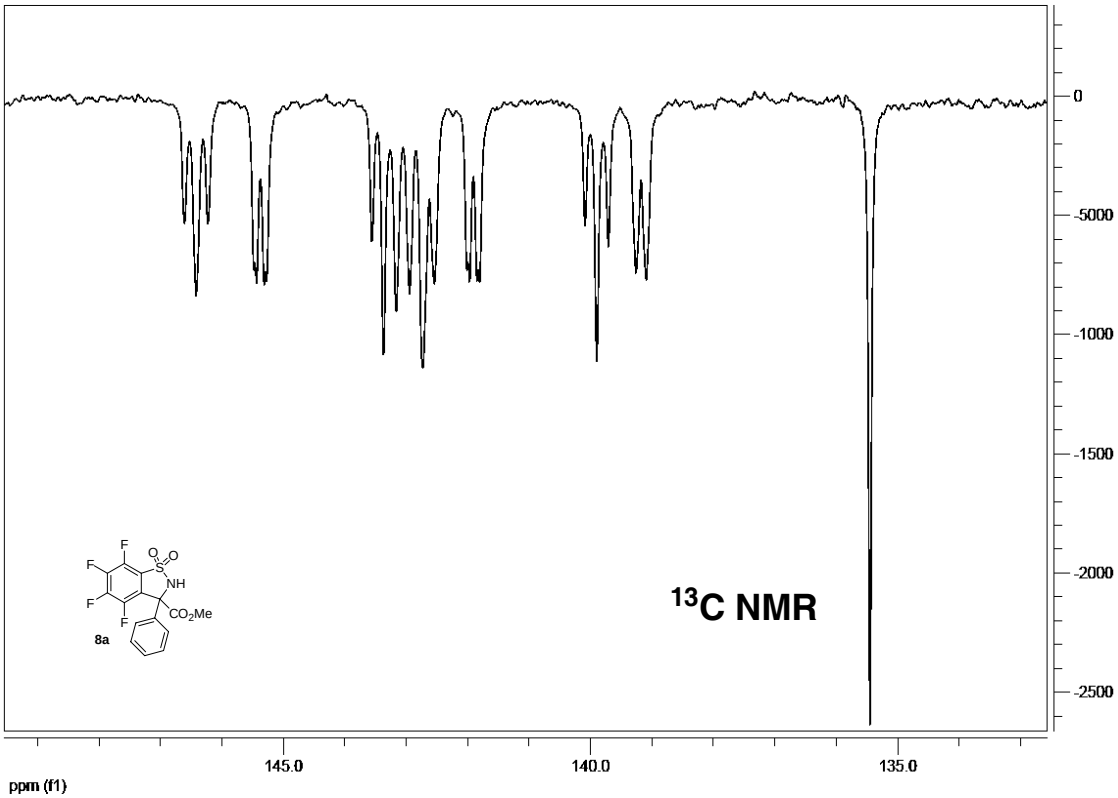

^{1}H NMR
7f
2.91
2.85
0.67
1.93
1.02
3.00
1.17
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

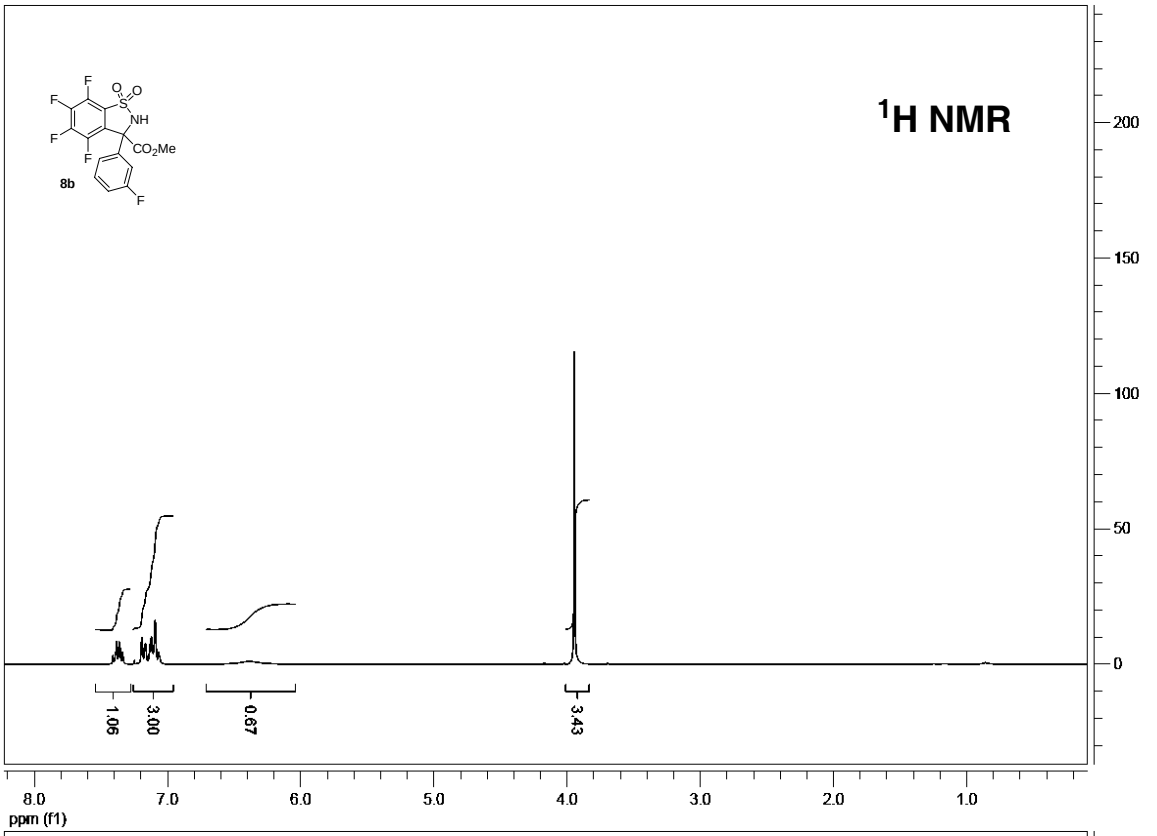

^{19}F NMR
7f
1.00
0.94
1.01
1.07
-130.0
-135.0
-140.0
-145.0
-150.0
-155.0
ppm (f1)

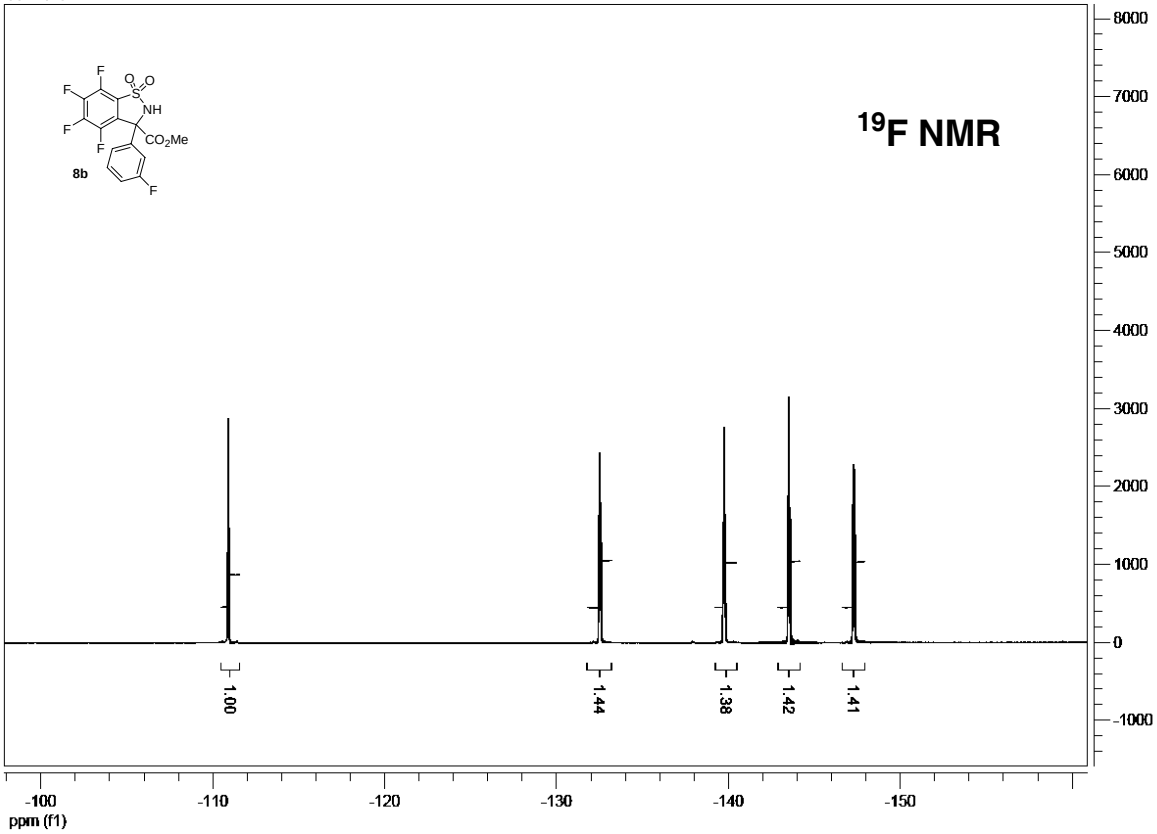

8a
^{1}H NMR
5.00
0.46
3.36
ppm (f1)

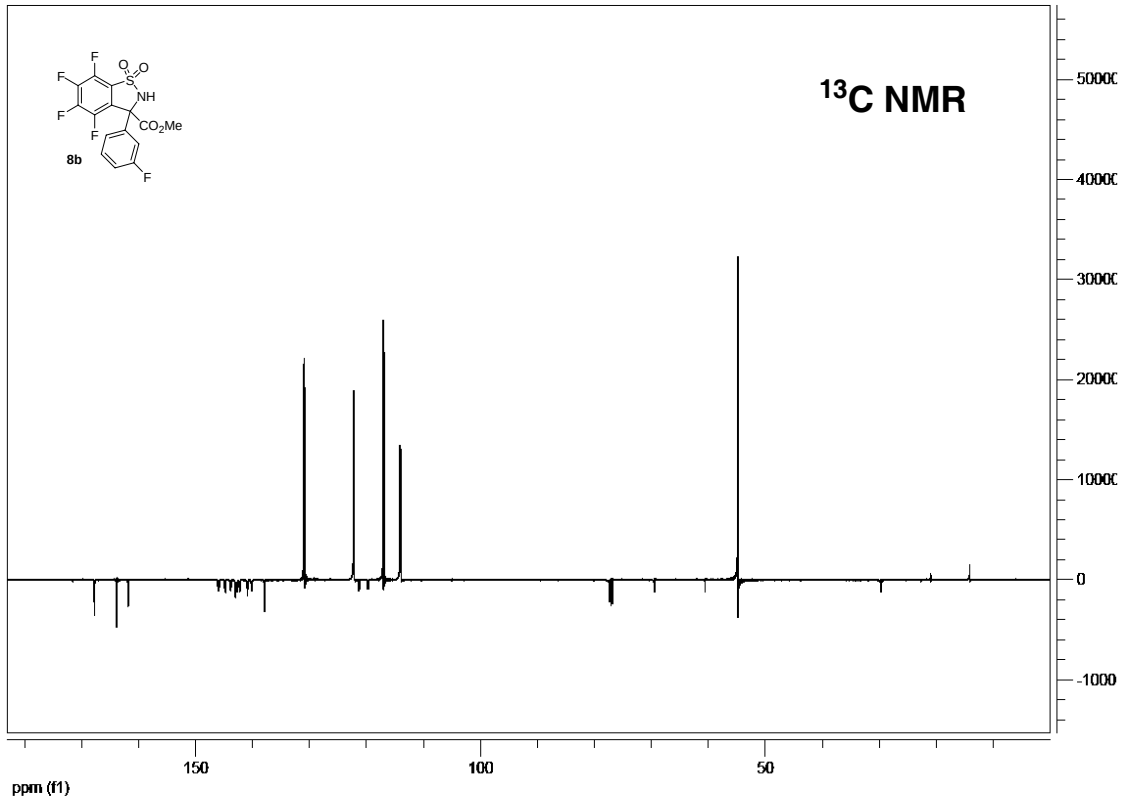

8a
^{19}F NMR
1.00
0.95
1.00
1.01
ppm (f1)

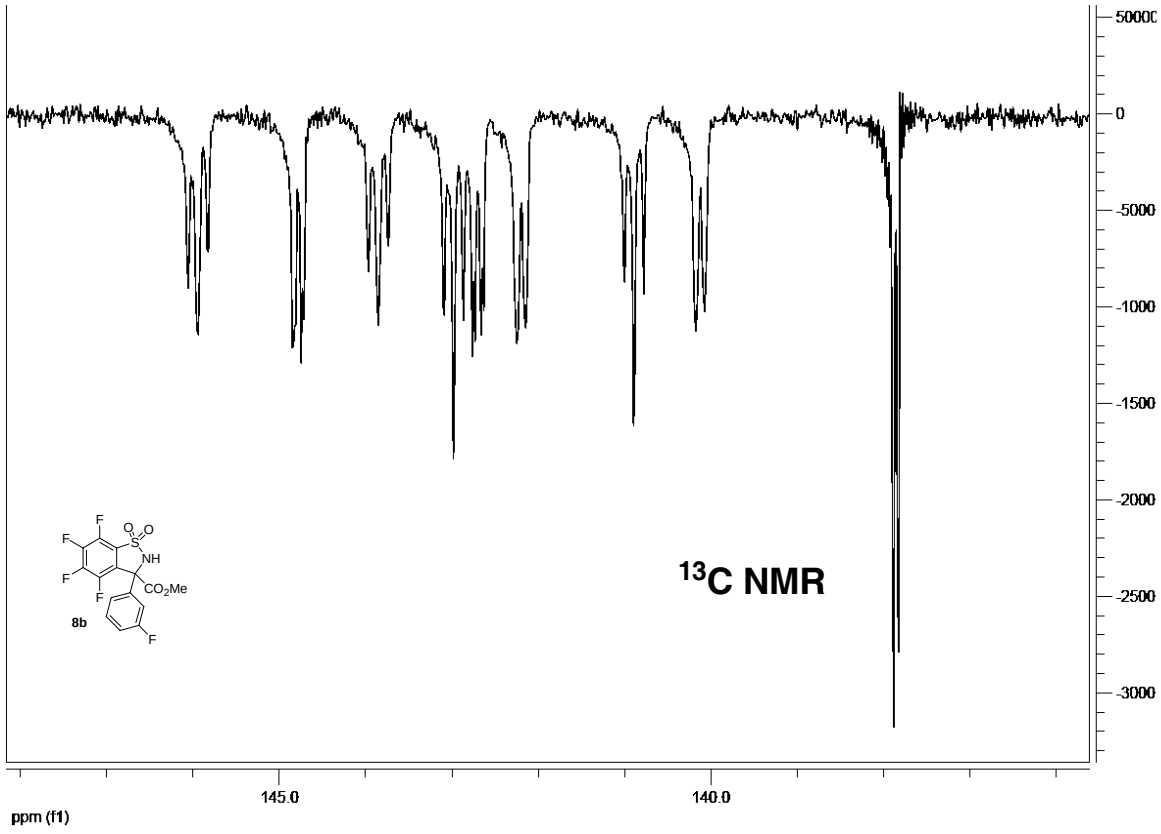

^{13}C NMR
8a
150
100
50
ppm (f1)

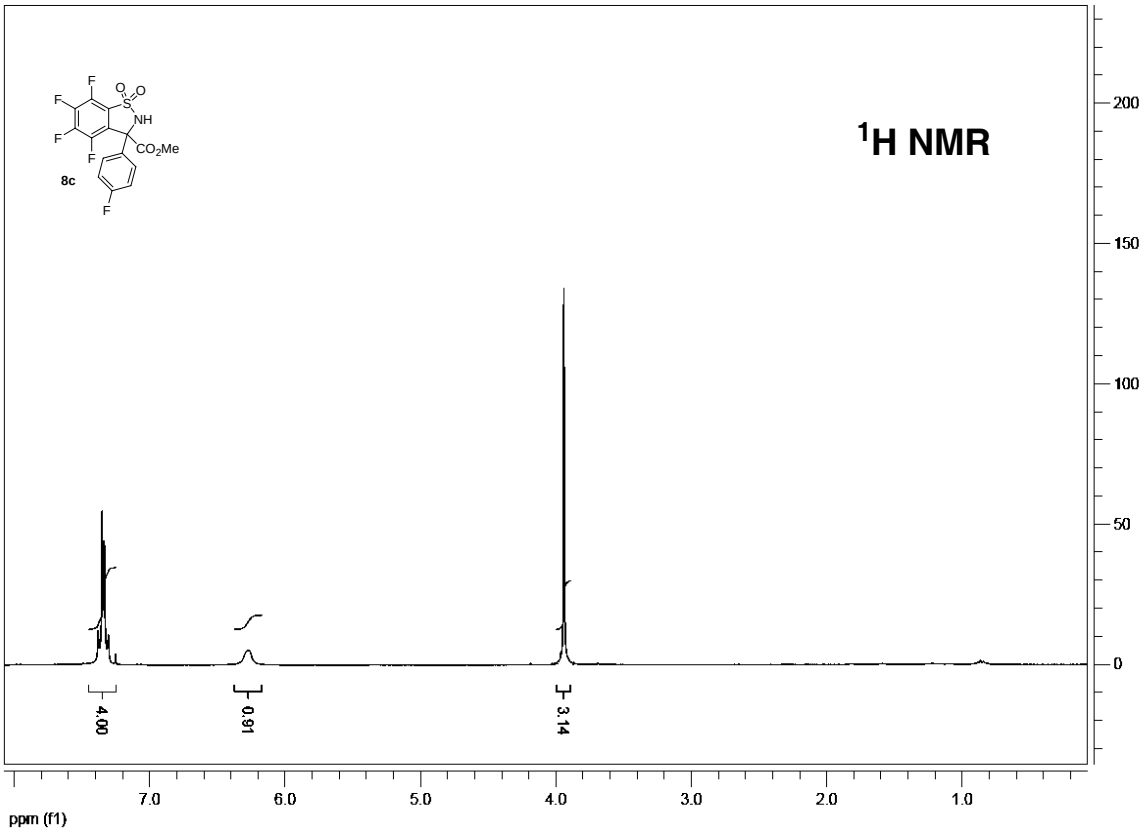

^{13}C NMR
8a
145.0
140.0
135.0
ppm (f1)

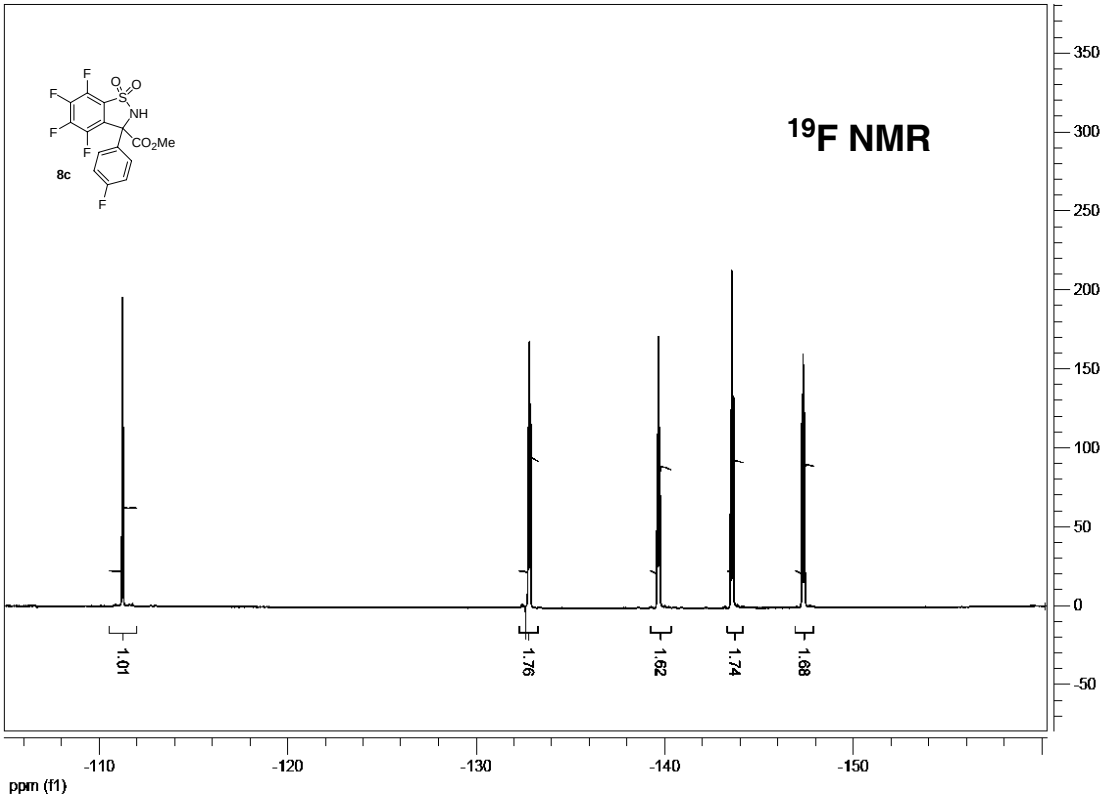

8b
^{1}H NMR
1.06
3.00
0.67
3.43
ppm (f1)

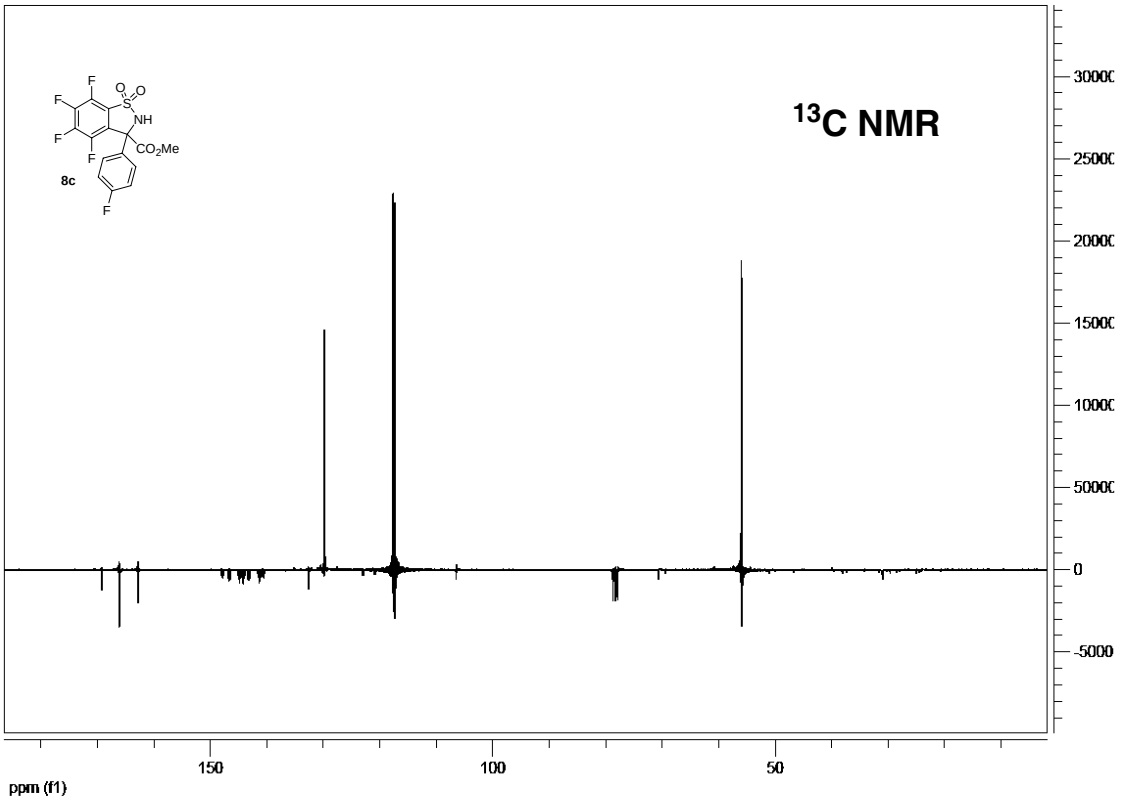

8b
^{19}F NMR
1.00
1.44
1.38
1.42
1.41
ppm (f1)

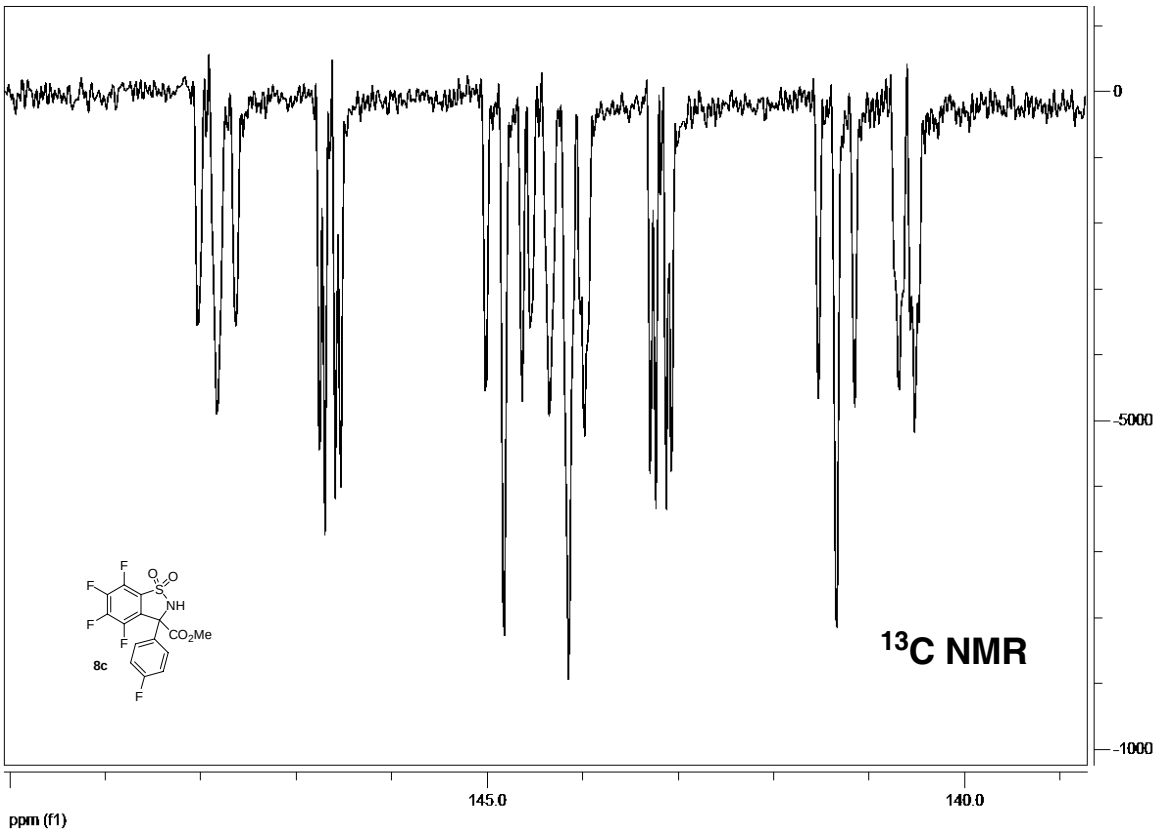

^{13}C NMR
8b
50000
40000
30000
20000
10000
0
-1000
150
100
50
ppm (f1)

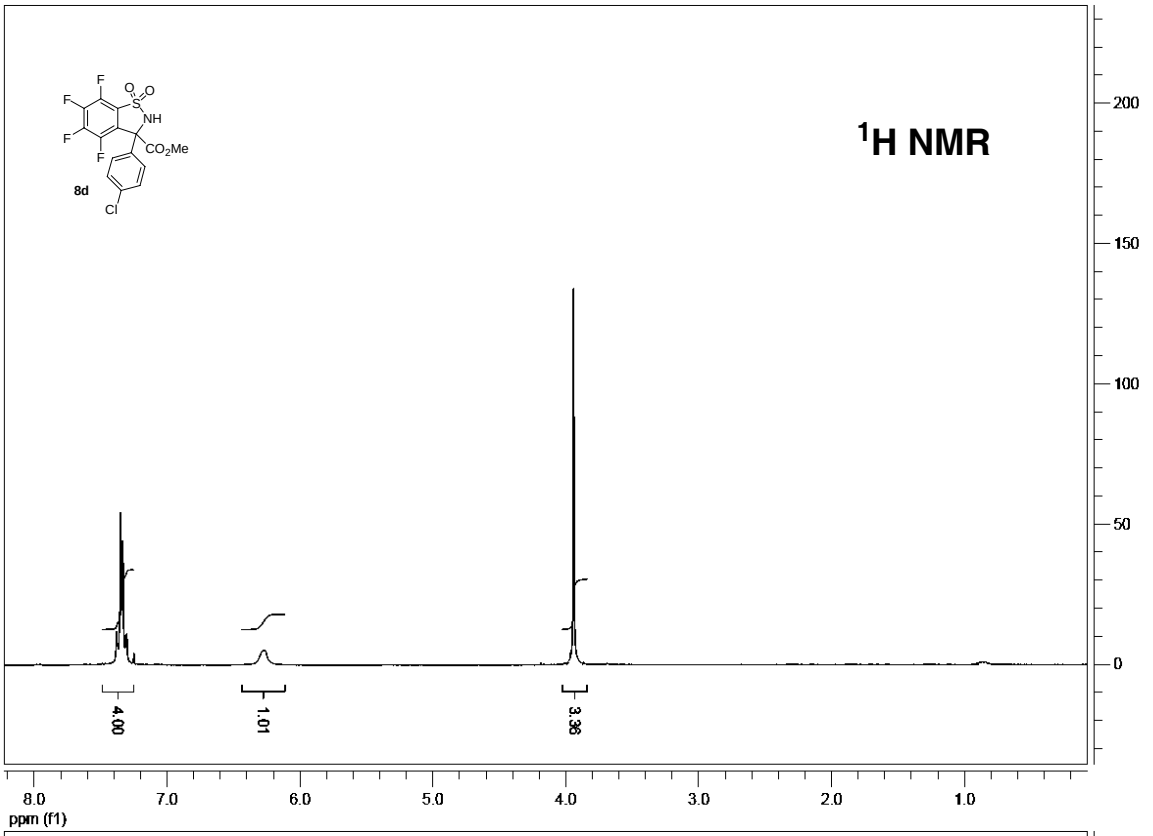

^{13}C NMR
8b
50000
0
-5000
-10000
-15000
-20000
-25000
-30000
145.0
140.0
ppm (f1)

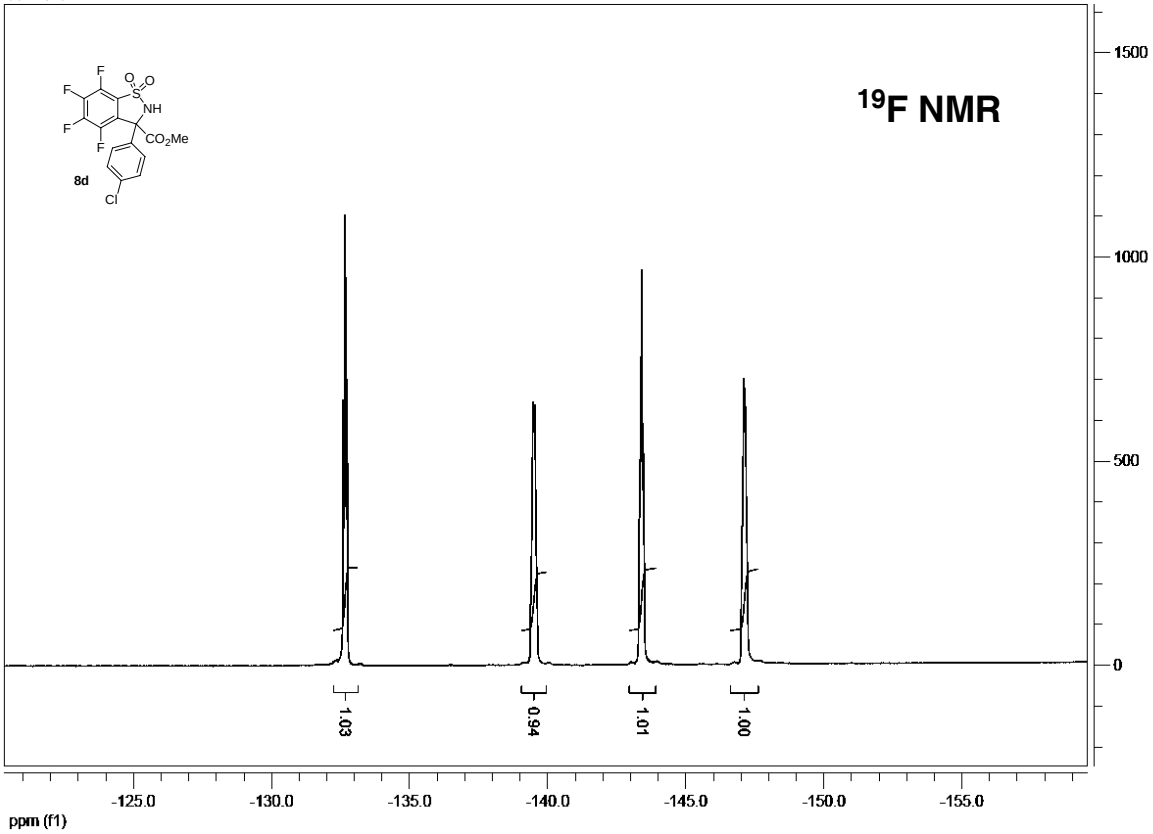

8c
^{1}H NMR
4.00
0.91
3.14
ppm (f1)

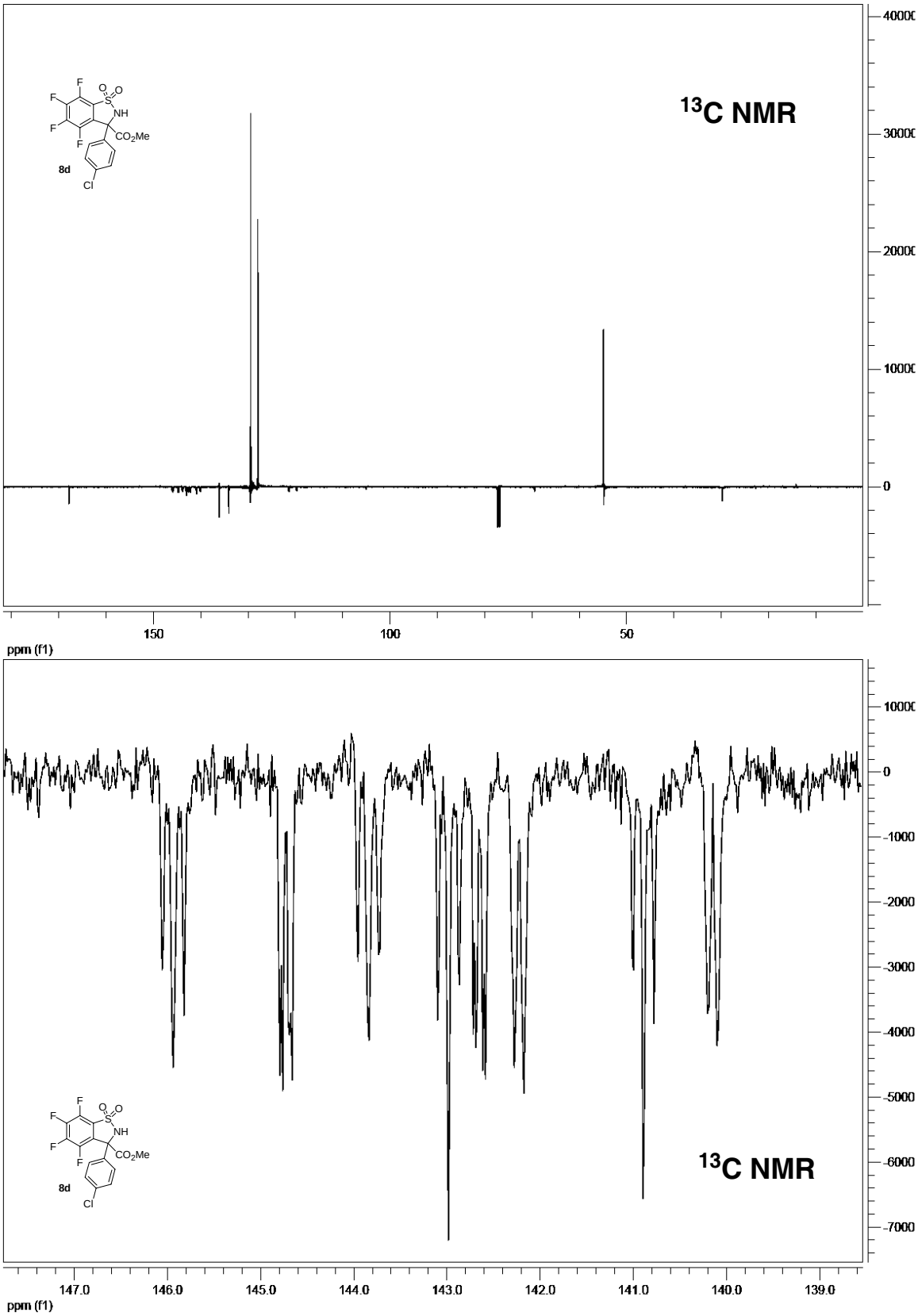

8c
^{19}F NMR
1.01
1.76
1.62
1.74
1.68
ppm (f1)

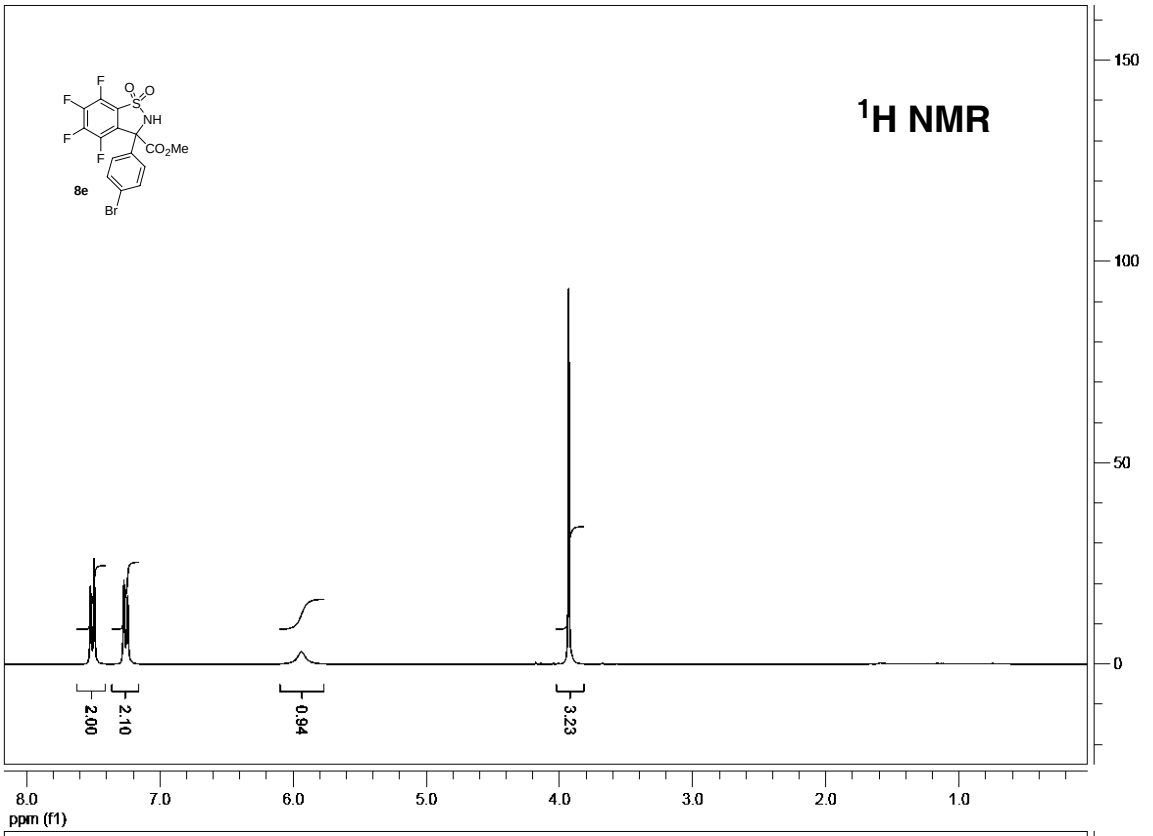

^{13}C NMR
8c
150
100
50
ppm (f1)

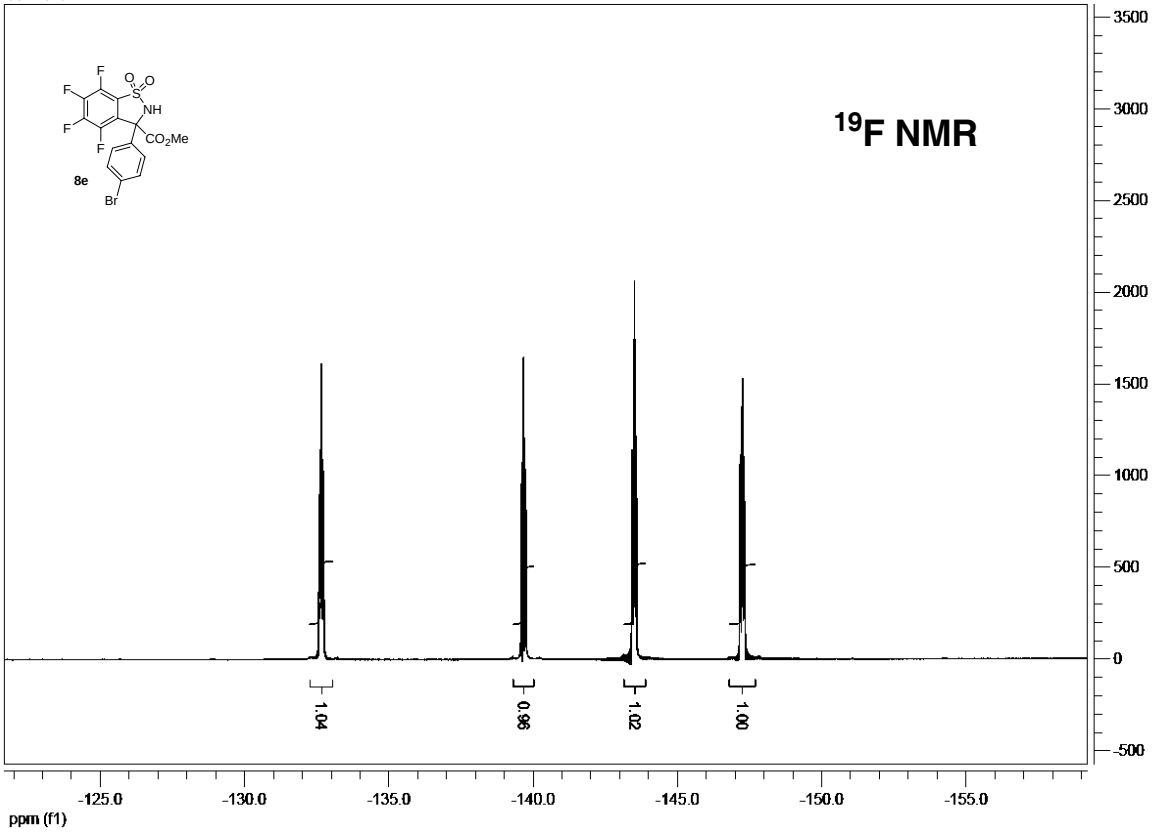

^{13}C NMR
8c
145.0
140.0
ppm (f1)

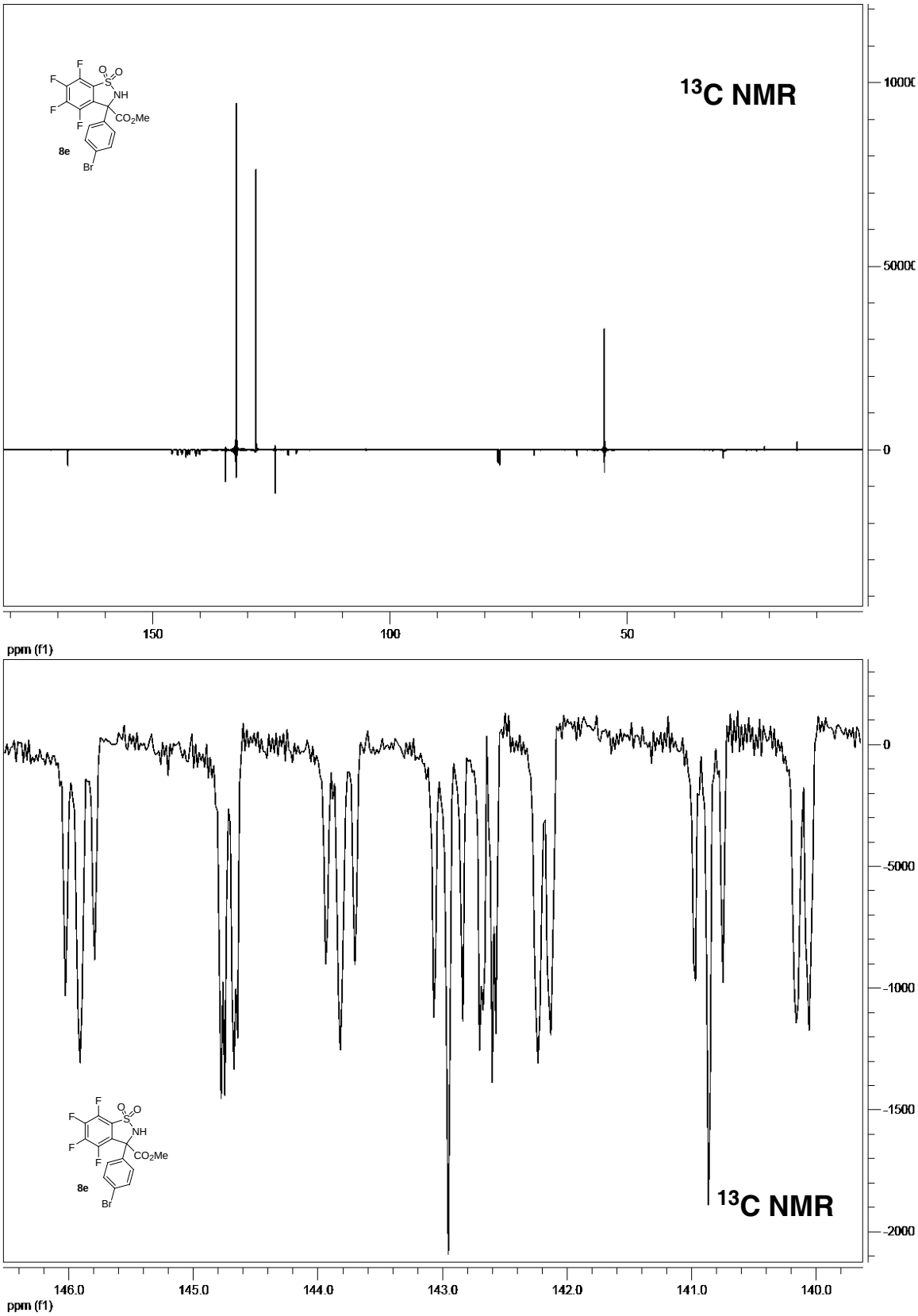

8d
^{1}H NMR
4.00
1.01
3.36
ppm (f1)

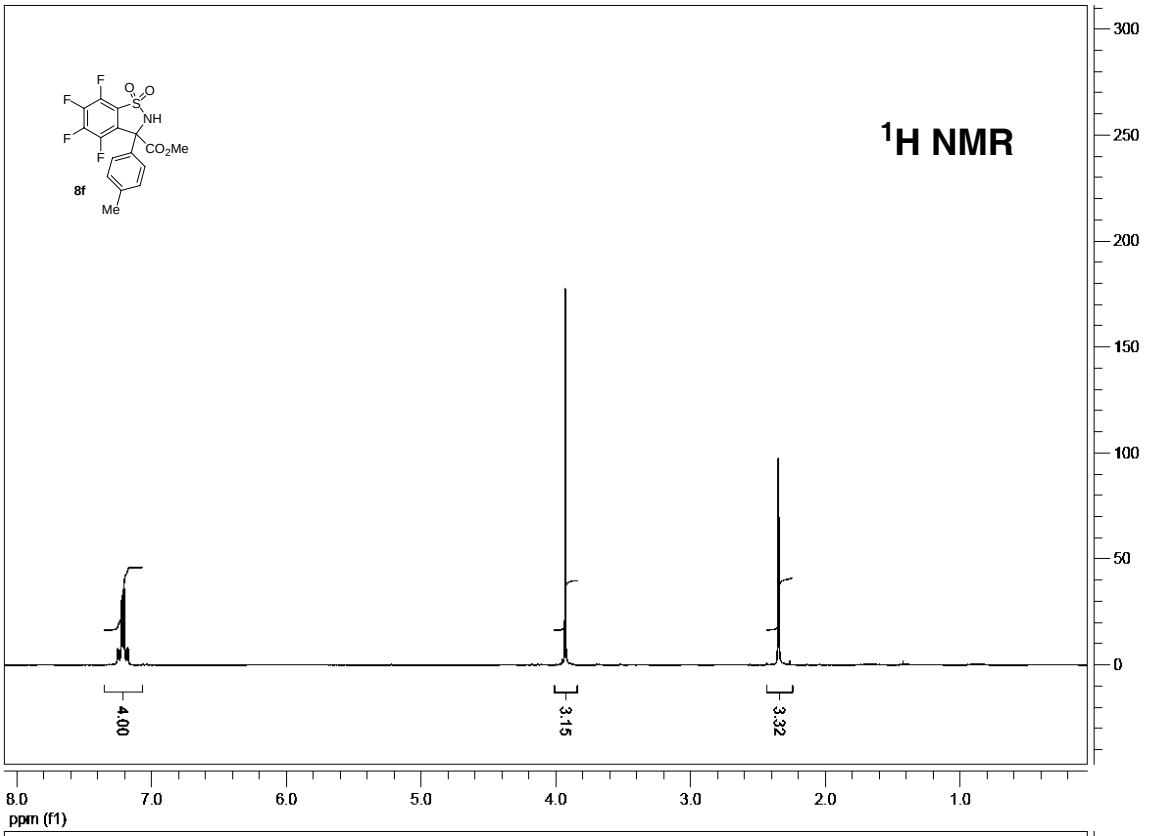

8d
^{19}F NMR
1.03
0.94
1.01
1.00
ppm (f1)

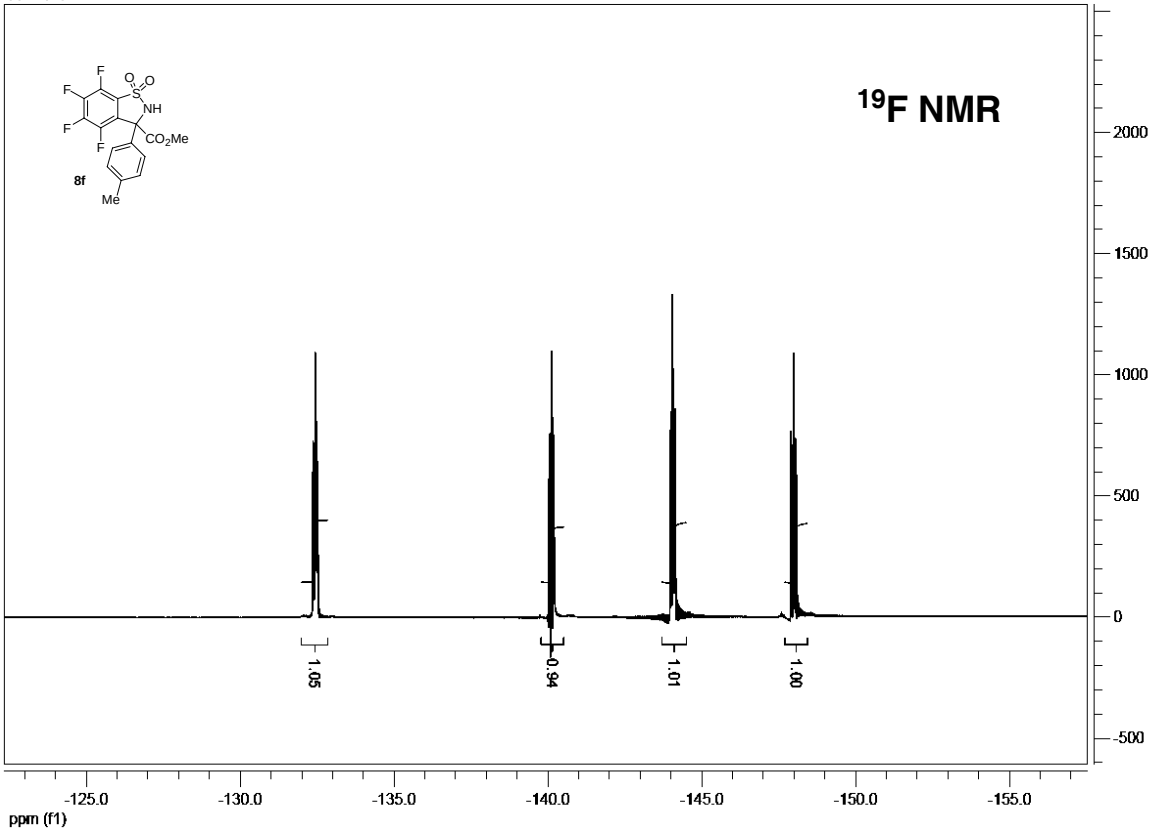

^{13}C NMR
8d
ppm (f1)
^{13}C NMR
8d
ppm (f1)

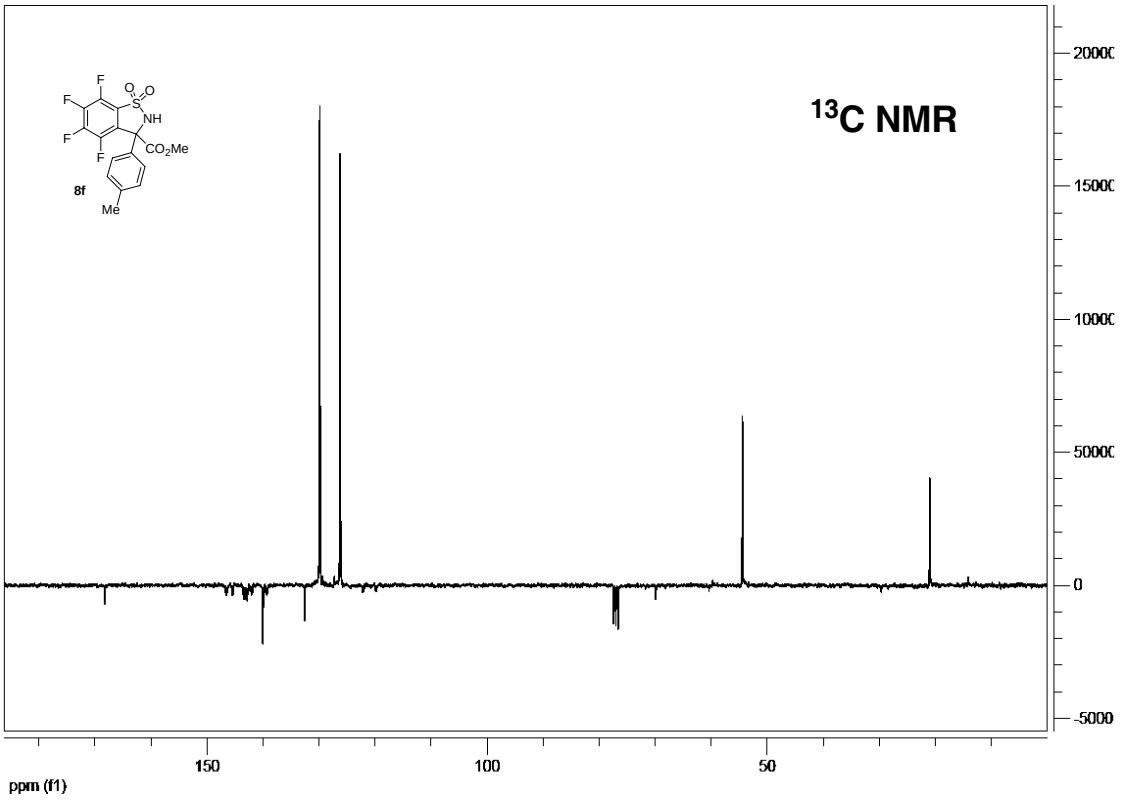

8e
^{1}H NMR
2.00
2.10
0.94
3.23
ppm (f1)

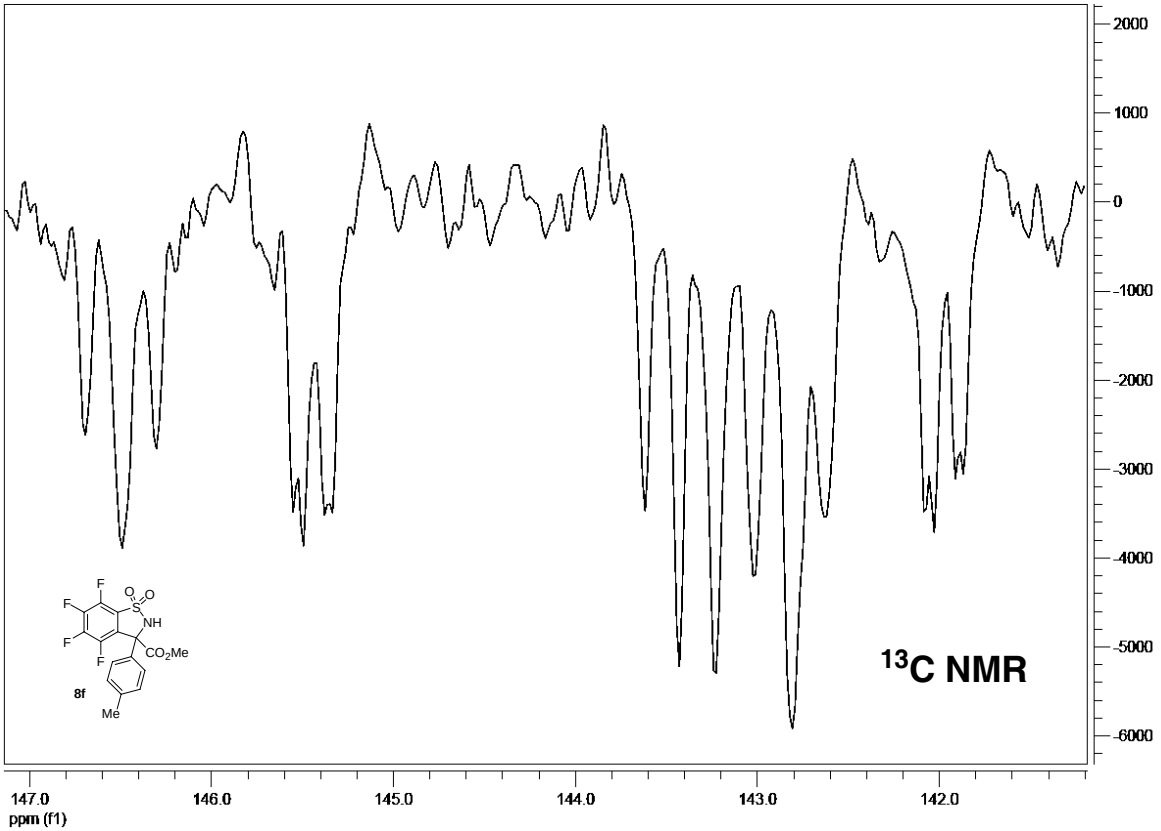

8e
^{19}F NMR
1.04
0.96
1.02
1.00
ppm (f1)

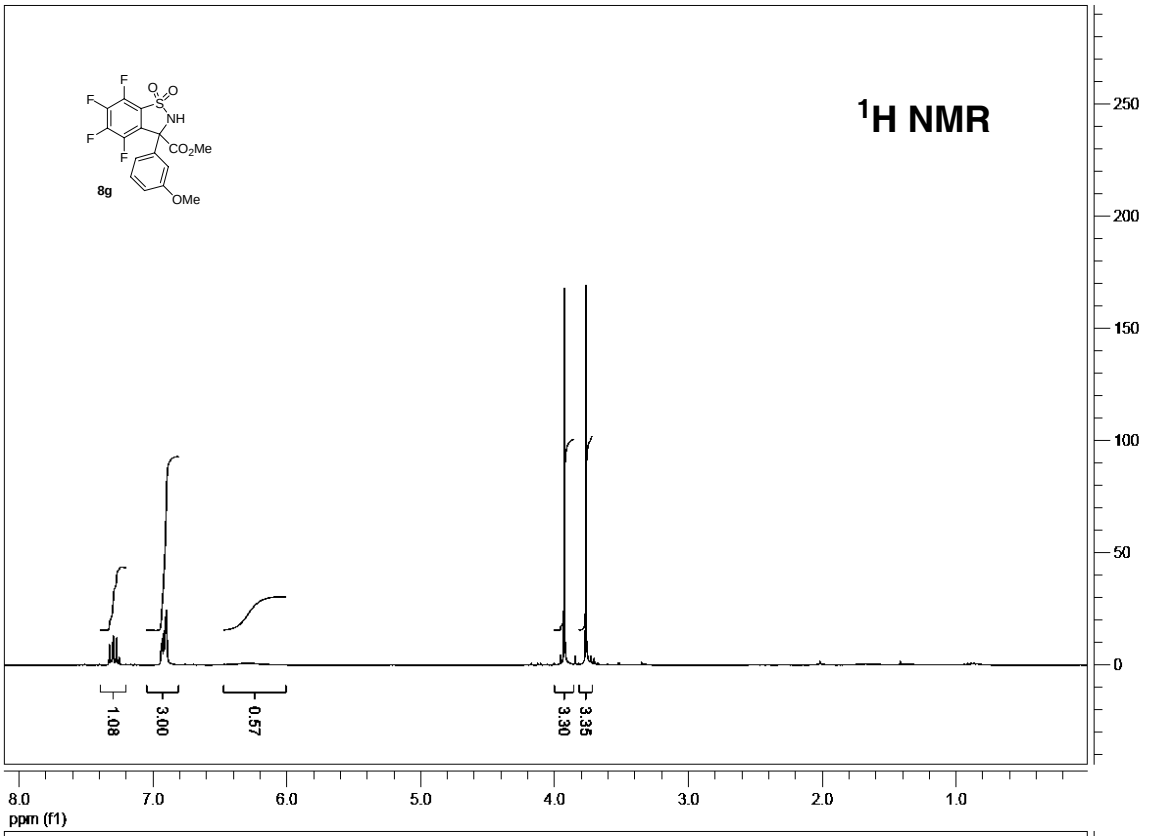

13C NMR
8e
10000
50000
0
150
100
50
ppm (f1)
0
-5000
-10000
-15000
-20000
146.0
145.0
144.0
143.0
142.0
141.0
140.0
ppm (f1)
13C NMR
8e

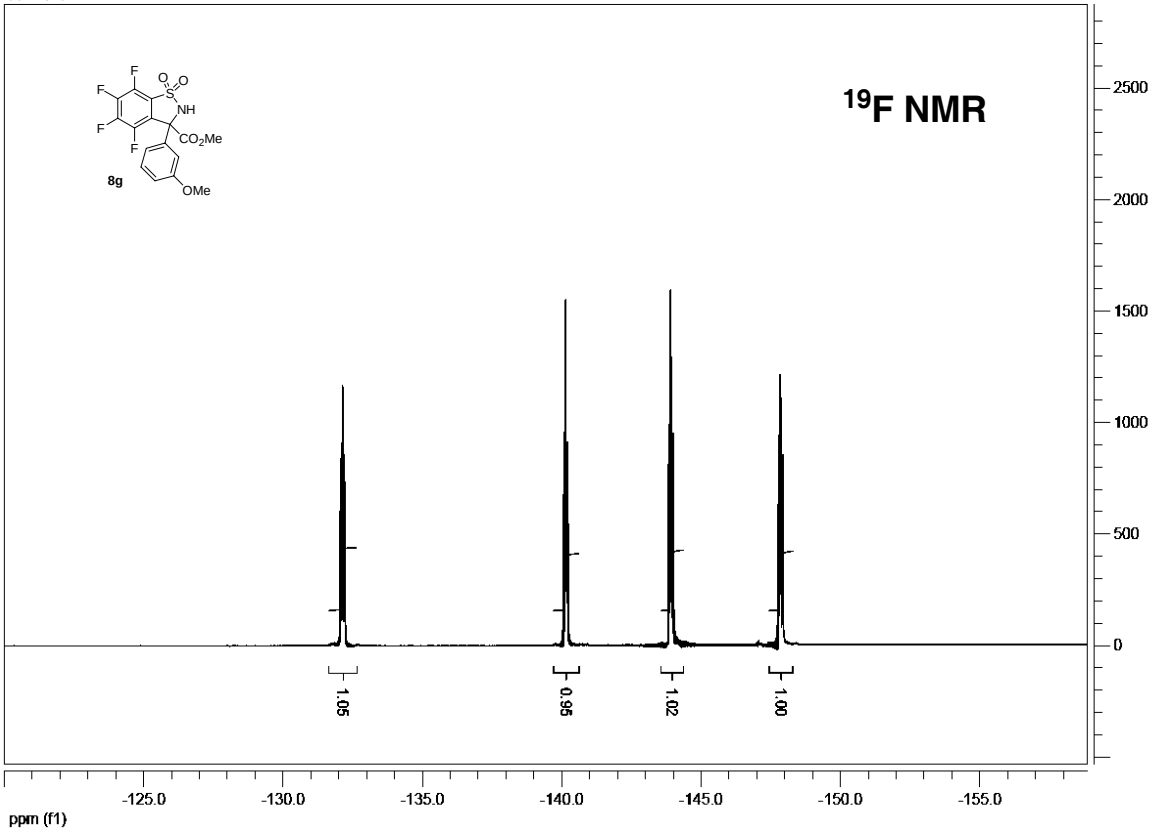

8f
Me
^{1}H NMR
4.00
3.15
3.32
ppm (f1)

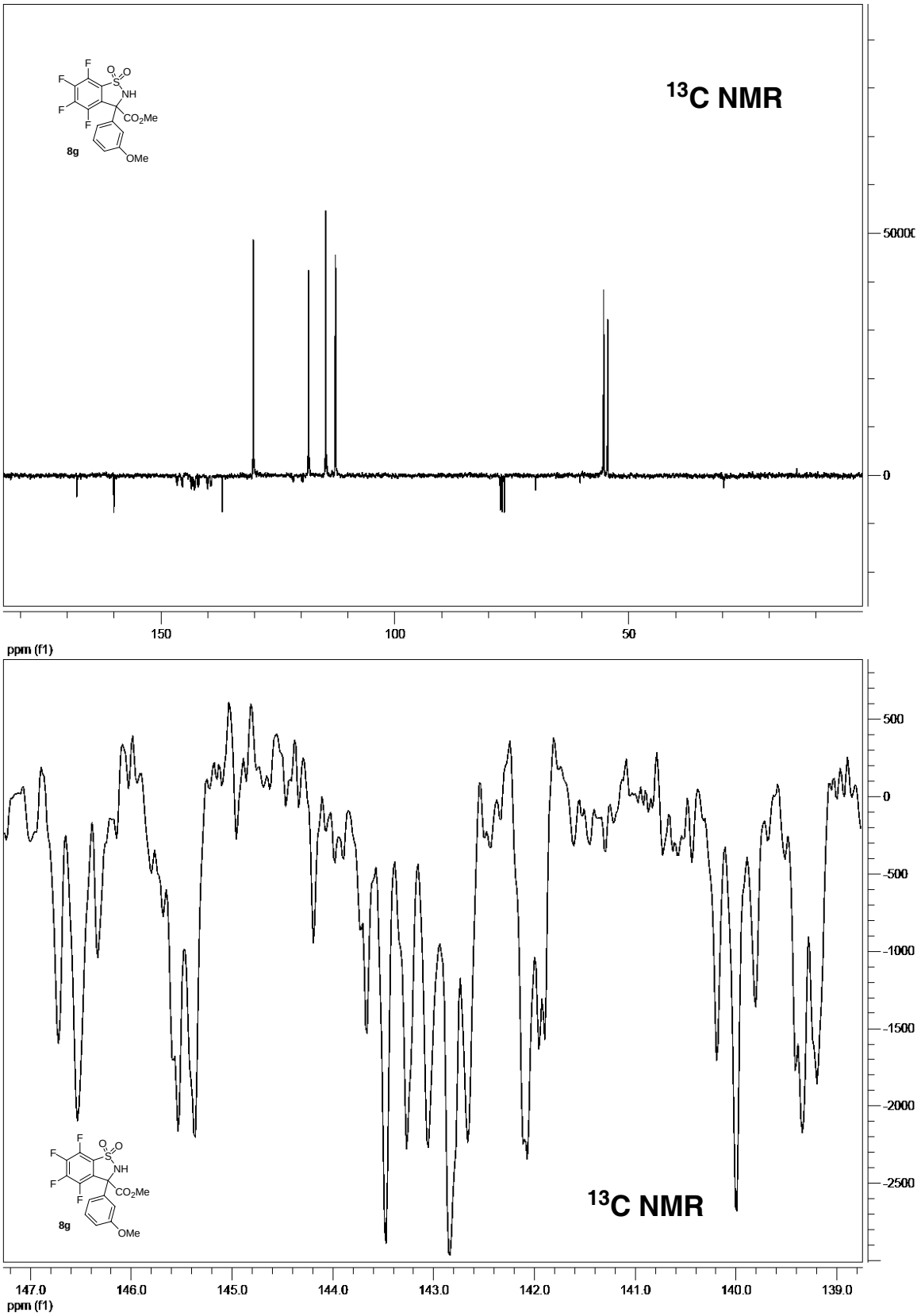

8f
Me
^{19}F NMR
1.05
0.94
1.01
1.00
ppm (f1)

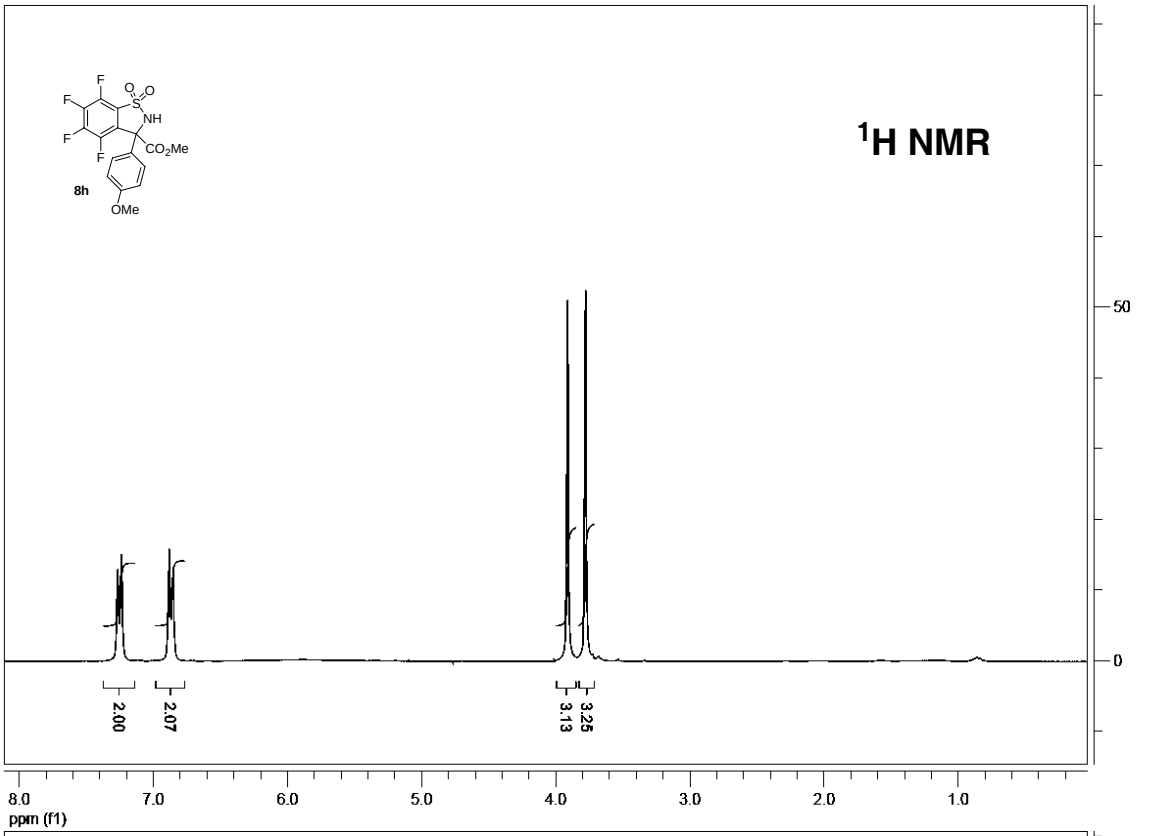

F
F
F
O
O
S
NH
CO2Me
8f
Me
13C NMR
20000
15000
10000
5000
0
-5000
150
100
50
ppm (f1)

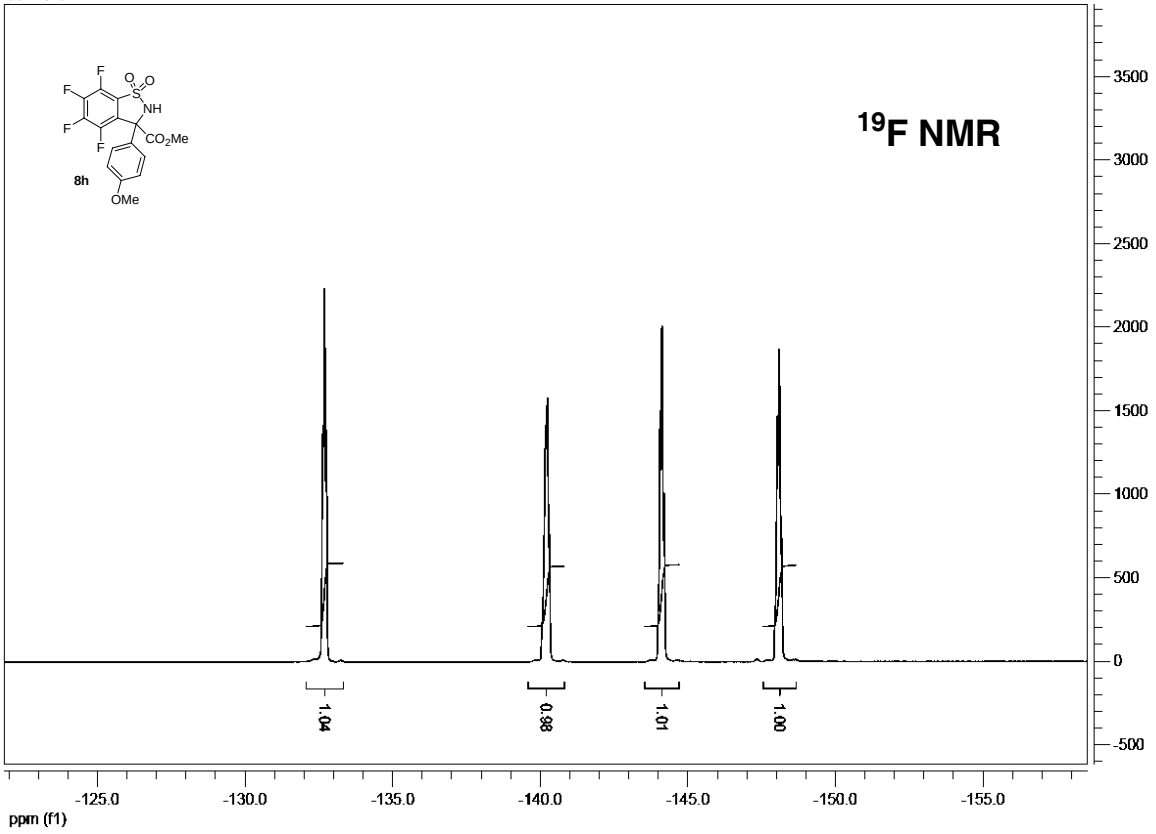

F
F
F
O
O
S
NH
CO2Me
8f
Me
13C NMR
2000
1000
0
-1000
-2000
-3000
-4000
-5000
-6000
147.0
146.0
145.0
144.0
143.0
142.0
ppm (f1)

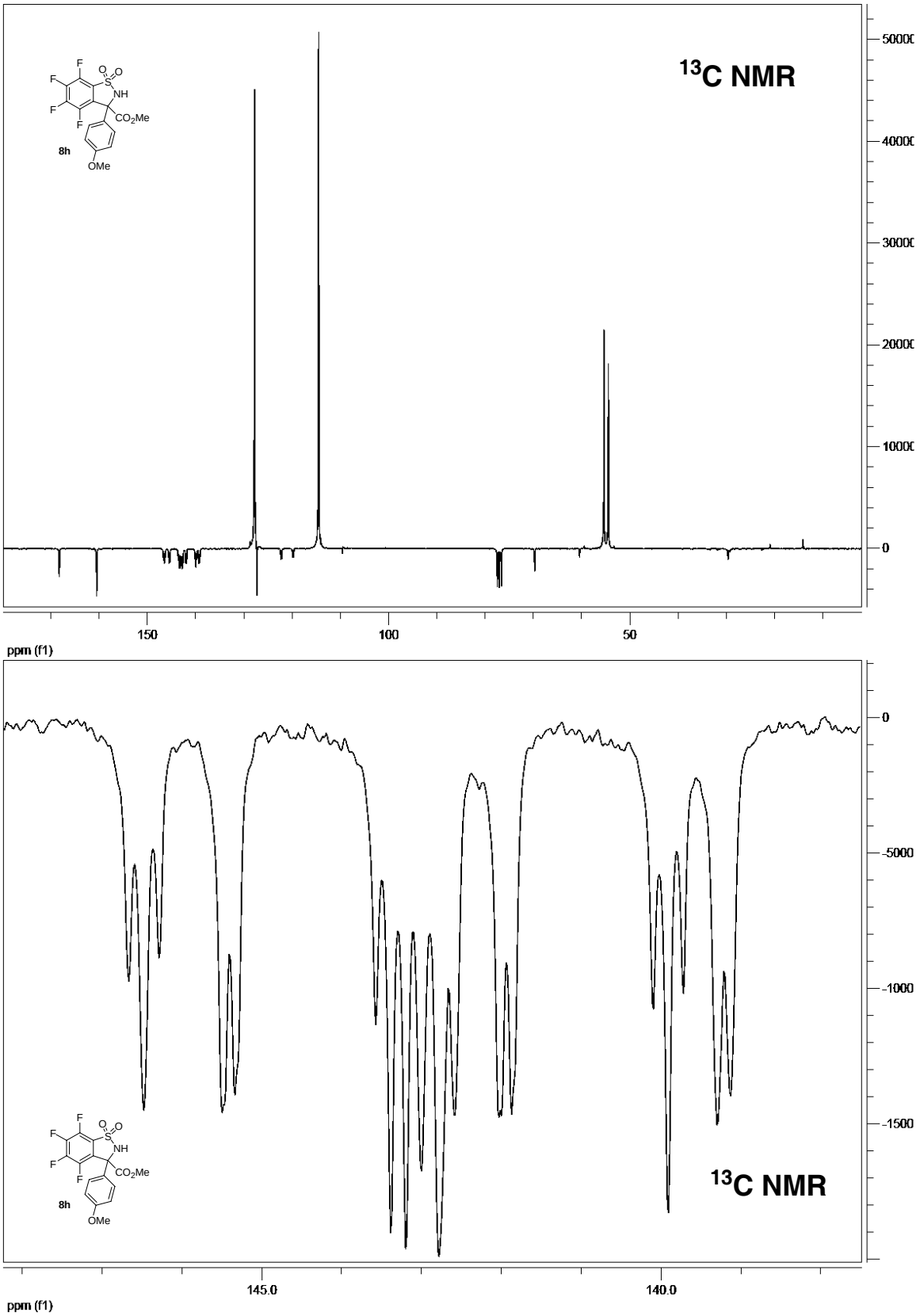

8g
^{1}H NMR
1.08
3.00
0.57
3.30
3.35
ppm (f1)

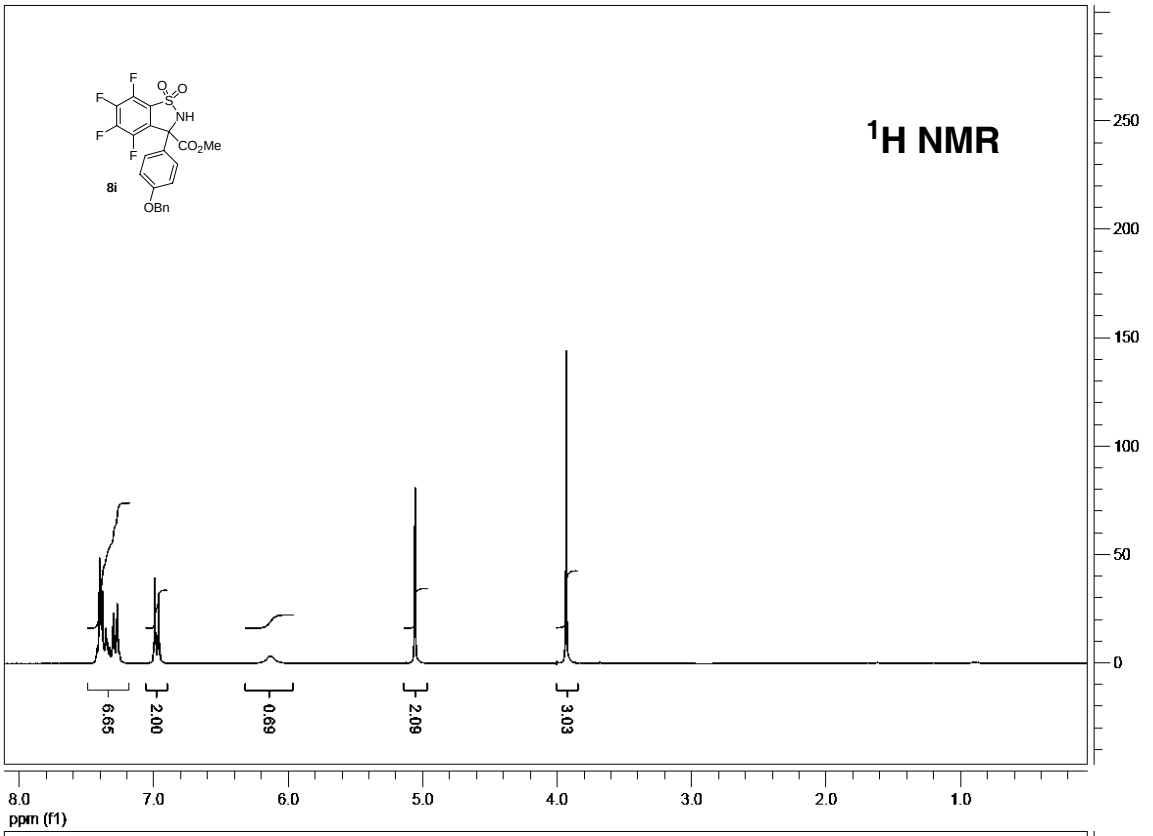

8g
^{19}F NMR
1.05
0.95
1.02
1.00
ppm (f1)

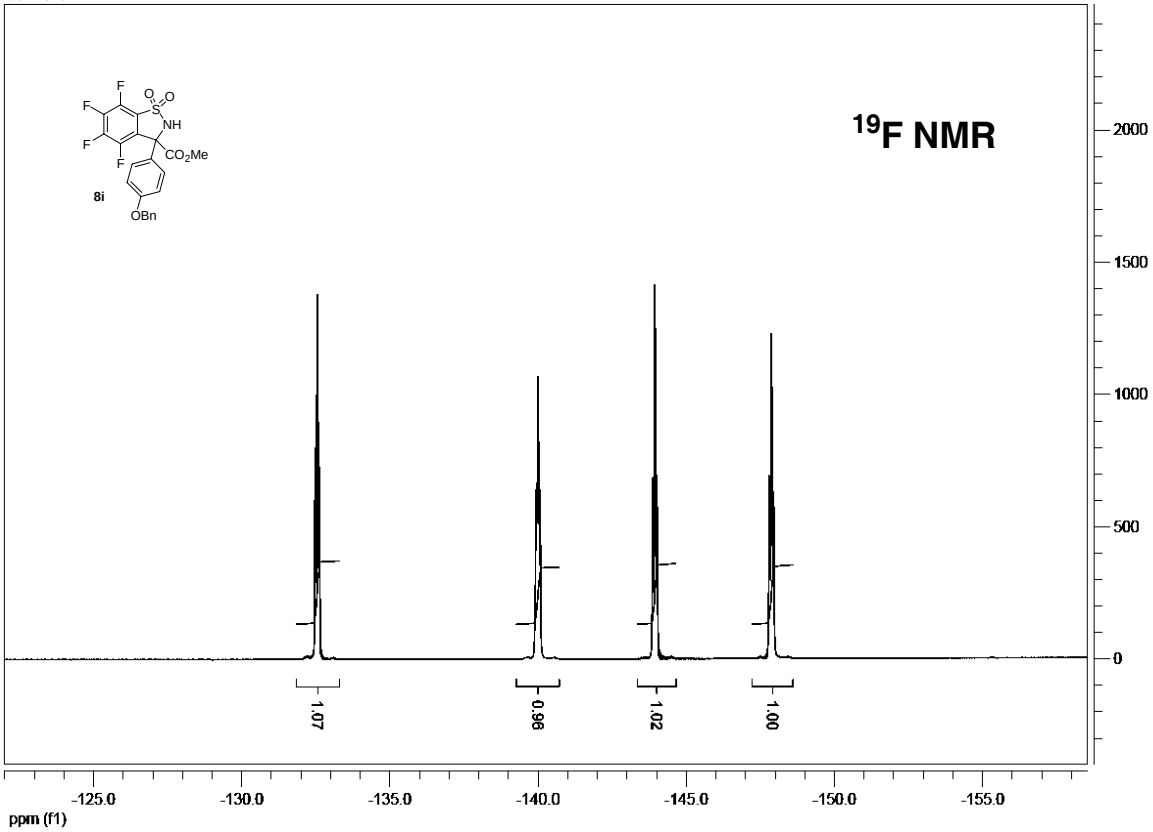

^{13}C NMR
8g
50000
0
150
100
50
ppm (f1)
500
0
-500
-1000
-1500
-2000
-2500
^{13}C NMR
8g
147.0
146.0
145.0
144.0
143.0
142.0
141.0
140.0
139.0
ppm (f1)

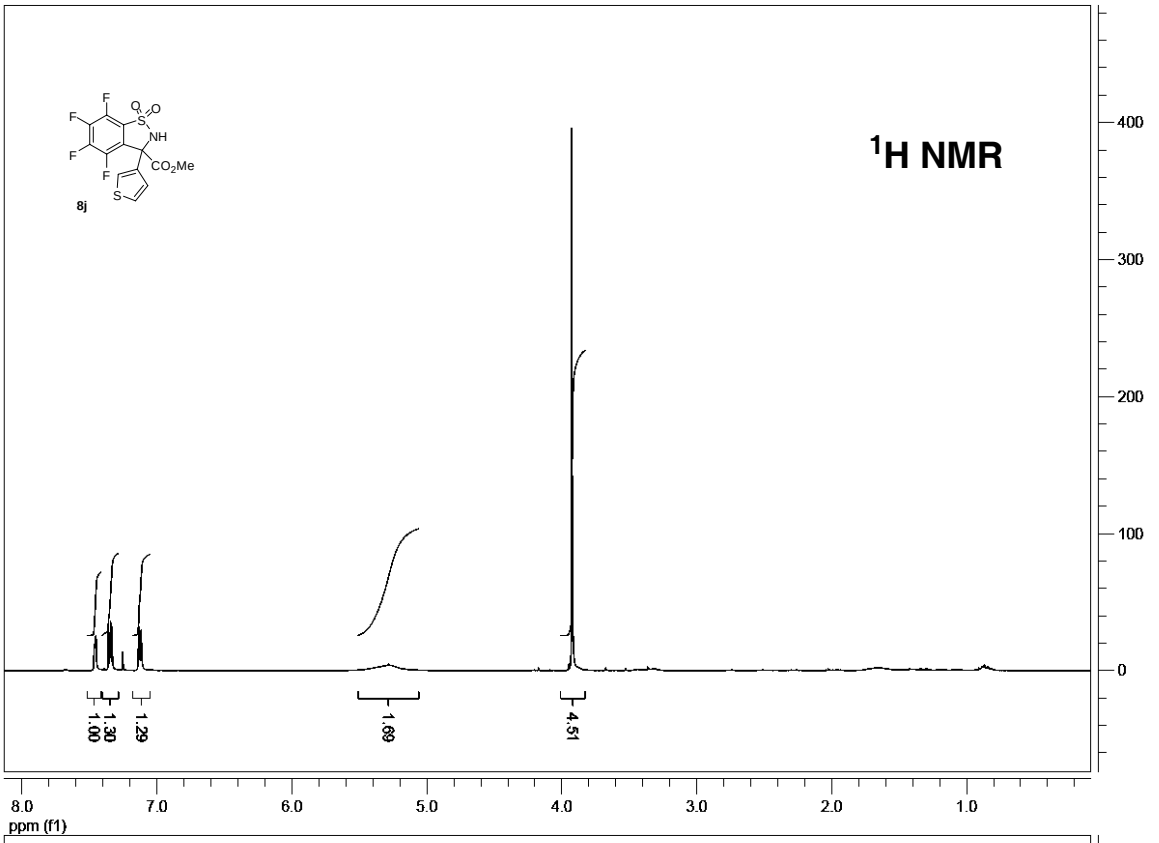

8h
^{1}H NMR
2.00
2.07
3.13
3.25
ppm (f1)

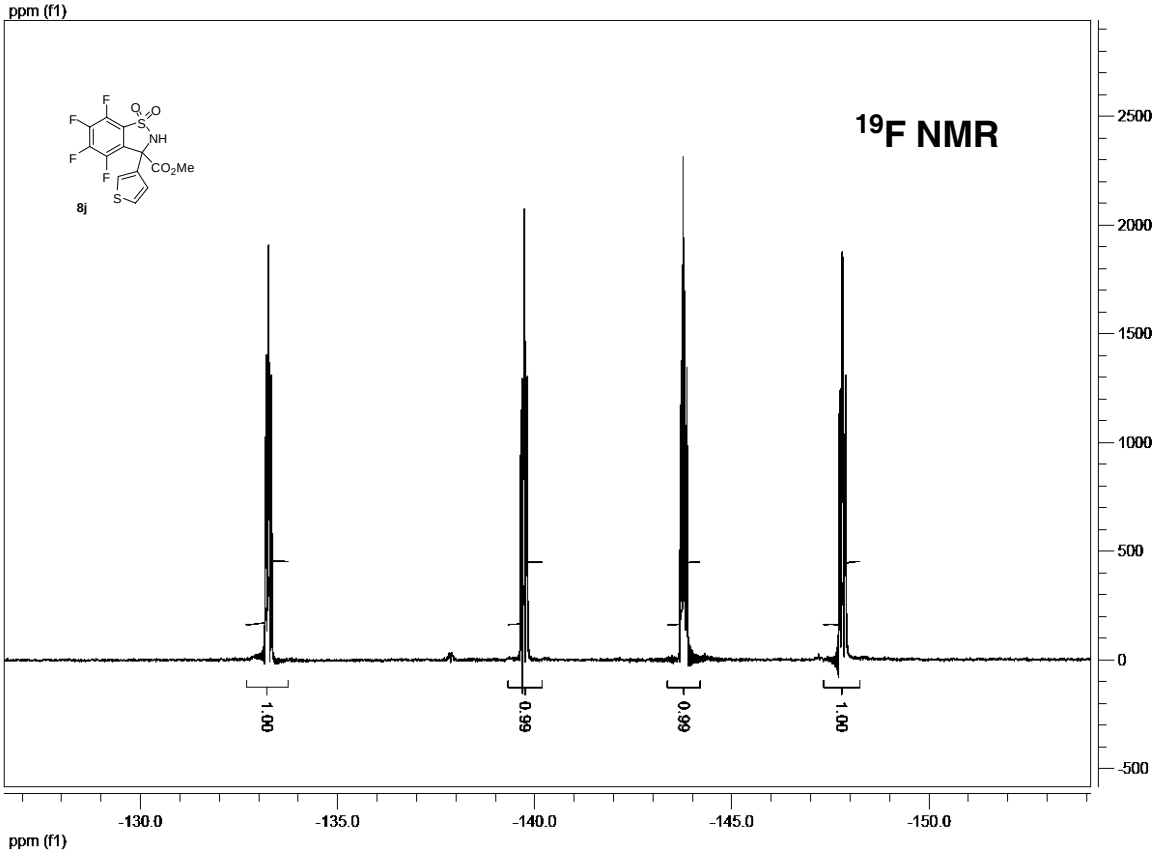

8h
^{19}F NMR
1.04
0.98
1.01
1.00
ppm (f1)

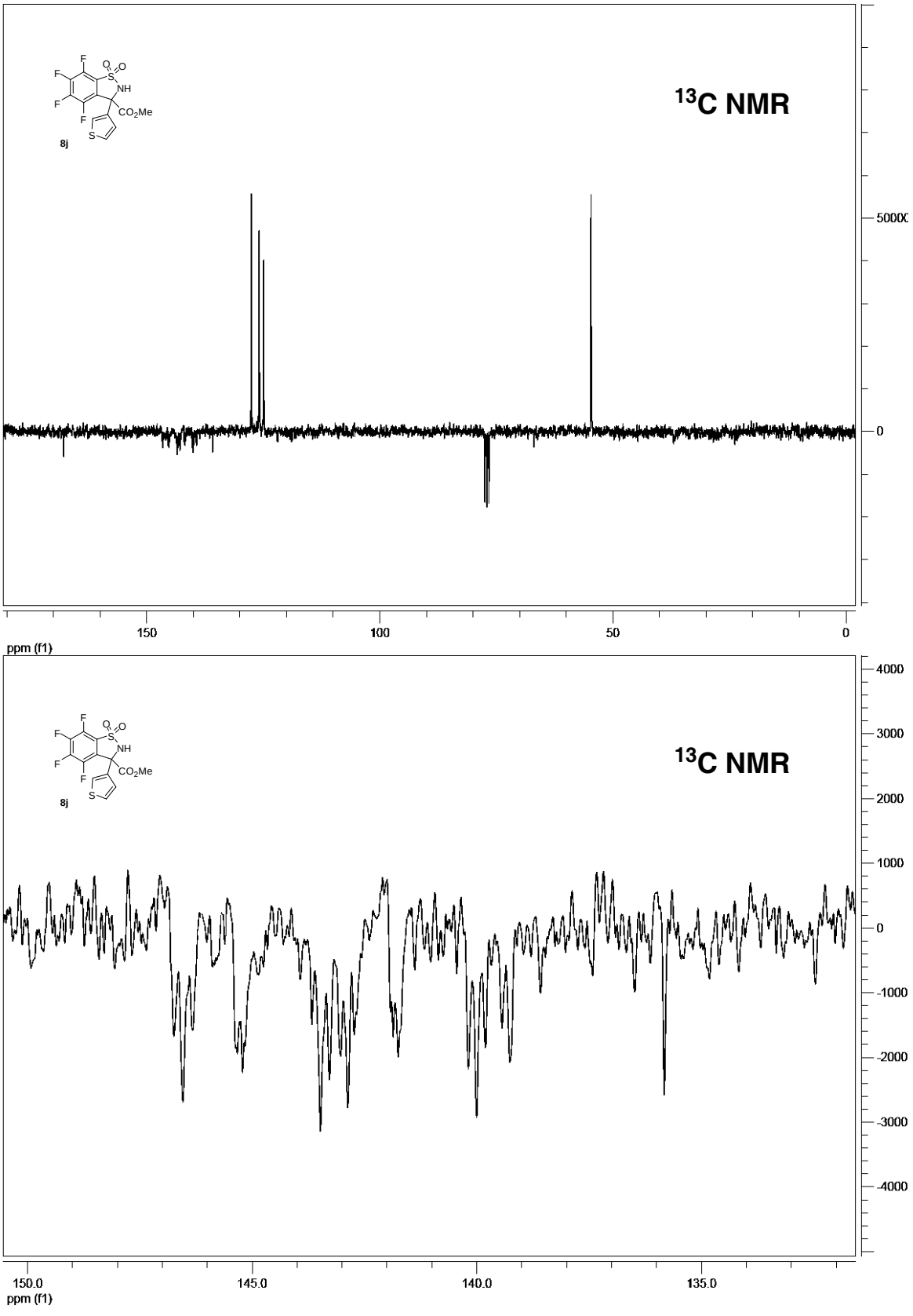

^{13}C NMR
8h
OMe
CO2Me
NH
150
100
50
ppm (f1)
^{13}C NMR
8h
OMe
CO2Me
NH
145.0
140.0
ppm (f1)


8i
^{1}H NMR
6.65
2.00
0.69
2.09
3.03
ppm (f1)

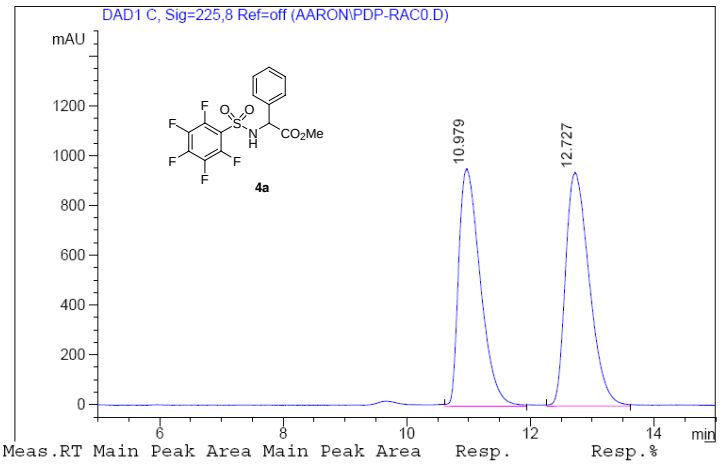

8i
^{19}F NMR
1.07
0.98
1.02
1.00
ppm (f1)


8j
^{1}H NMR
1.00
1.30
1.29
1.69
4.51
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)
400
300
200
100
0


8j
^{19}F NMR
1.00
0.99
0.99
1.00
-130.0
-135.0
-140.0
-145.0
-150.0
ppm (f1)
2500
2000
1500
1000
500
0
-500

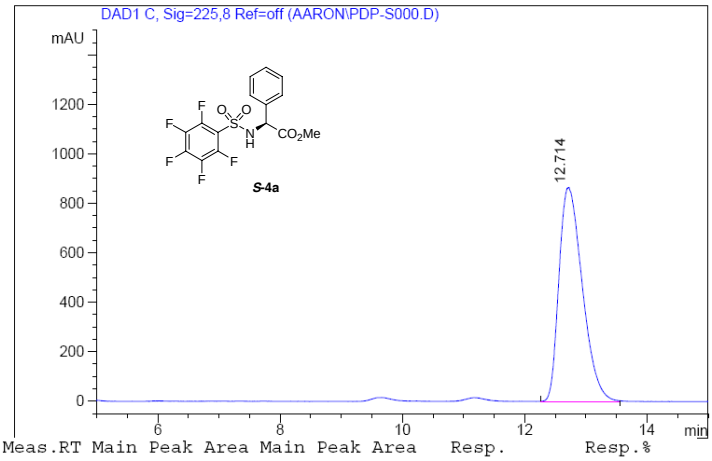

8j
^{13}C NMR
5000
0
150
100
50
0
ppm (f1)
8j
^{13}C NMR
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
150.0
145.0
140.0
135.0
ppm (f1)

```
data acquired by:  Aaron
on:                25/03/2008
Sample Info        PDP Racemo
                   Chiralpak OD, Hex/IPA 8:2 + 0.2 TFA 0.7 ml/min, 9
                   bar
```



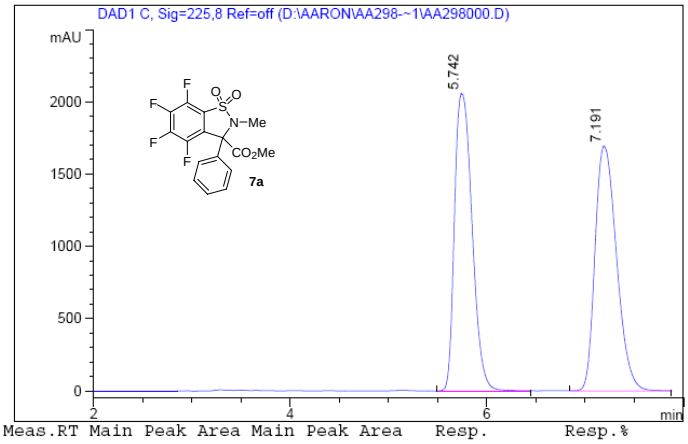
Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
10.979	23207.906	48.018	23207.906	48.018
12.727	25124.059	51.982	25124.059	51.982

```
data acquired by:  Aaron
on:                25/03/2008
Sample Info        PDP isomero S (+)
                   Chiralpak OD, Hex/IPA 8:2 + 0.2 TFA 0.7 ml/min, 9
                   bar
```



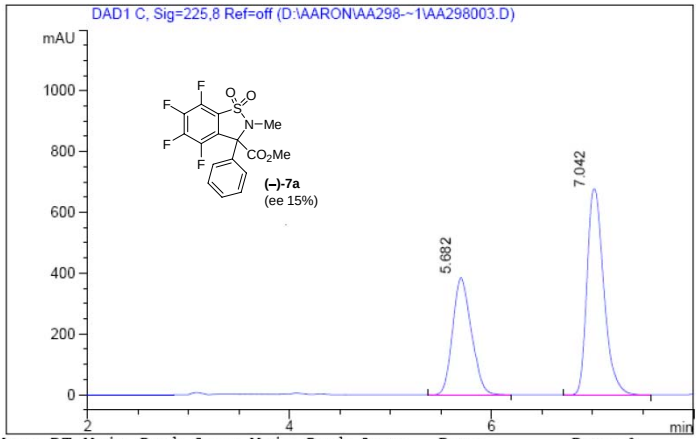
Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
12.714	23042.418	100.000	23042.418	100.000

```
data acquired by:  Aaron
on:                29/10/2007
Sample Info        AA 298   Campione A
                   chiralpak OD Hex/iPrOH 85:15 1ml/min 14bar
```

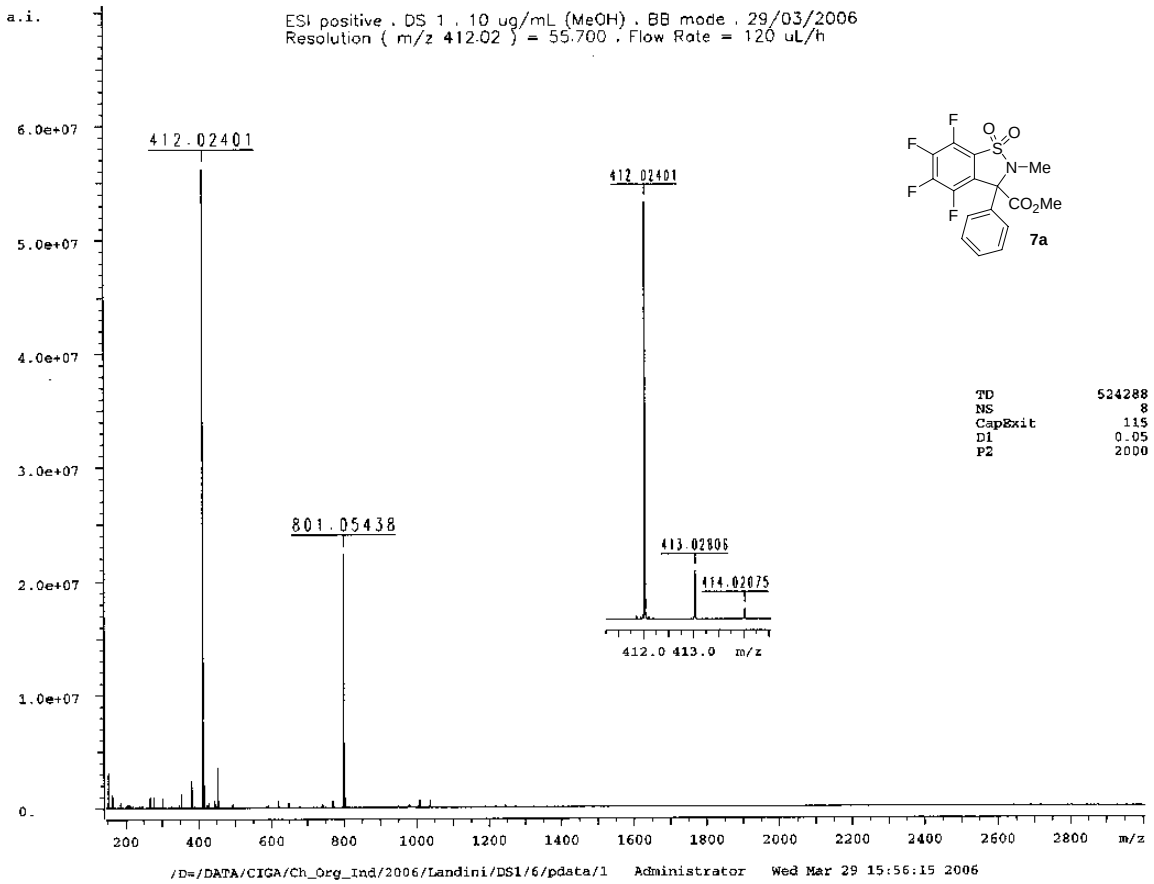


Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
5.742	25625.982	49.838	25625.982	49.838
7.191	25792.131	50.162	25792.131	50.162

```
data acquired by:  Aaron
on:                29/10/2007
Sample Info        AA 298   Campione C
                   chiralpak OD Hex/iPrOH 85:15 1ml/min 14bar
```



Meas.RT	Main Peak Area	Main Peak Area	Resp.	Resp.%
5.682	5327.307	42.288	5327.307	42.288
7.042	7270.282	57.712	7270.282	57.712


a.i.
ESI positive , DS 1 , 10 ug/mL (MeOH) , BB mode , 29/03/2006
Resolution (m/z 412.02) = 55.700 , Flow Rate = 120 uL/h
412.02401
801.05438
412.02401
413.02806
414.02075
412.0 413.0 m/z
F
F
F
O
O
S
N–Me
CO2Me
7a
TD 524288
NS 8
CapExit 115
D1 0.05
P2 2000
6.0e+07
5.0e+07
4.0e+07
3.0e+07
2.0e+07
1.0e+07
0.
200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400 2600 2800 m/z
/D=/DATA/CIGA/Ch_Org_Ind/2006/Landini/DS1/6/pdata/1 Administrator Wed Mar 29 15:56:15 2006